THE SYNTHESIS OF dl-DIHYDRODIDEOXYSTREPTOSE AND RELATED COMPOUNDS

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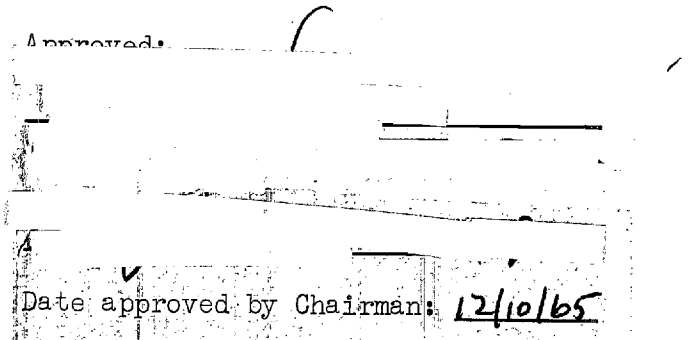

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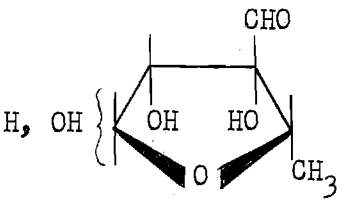
GLOSSARY OF ABBREVIATIONS

A.I.P.	Argon Inlet Pressure (GLC).
C.C.D.	Countercurrent distribution.
C.T.	Column Temperature (GLC).
DSS	Sodium 2,2-dimethyl-2-silapentane-5-sulfonate, n.m.r. standard.
EGSS-X	Ethylene glycol succinate polyester, GLC column liquid phase.
GLC	Gas-liquid chromatography.
QF-1	Fluorosilacone GLC column liquid phase.
R.T.	Retention Time (GLC).
SE-30	Silacone GLC column liquid phase.
TLC	Thin-layer chromatography.
TMS	Tetramethylsilane, n.m.r. standard.

SUMMARY

The antibiotic streptomycin has been shown to consist of streptidine (that isomer of 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane that has all groups equatorial), glycosidically attached through C_4 to C_1 of streptose (3-C-formyl-5-deoxy-L-lyxofuranose), which is in turn glycosidically attached through C_2 to C_1 of 2-deoxy-2-methylamino-L-glucopyranose. Both glycosidic attachments have been assigned the α configuration. Syntheses of streptidine and 2-deoxy-2-methylamino-L-glucopyranose were achieved many years ago. A recently reported synthesis of L-streptose (I) in these laboratories firmly established the structure of streptose and the absolute stereochemistry at C_2 and C_4. That synthesis did not unequivocally establish the stereochemistry at C_3. The purpose of this research was to effect a definitive synthesis of L-dihydrodideoxystreptose (II), a transformation product of streptose in streptomycin.



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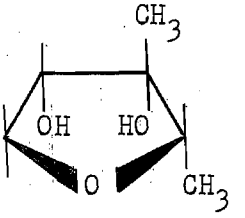
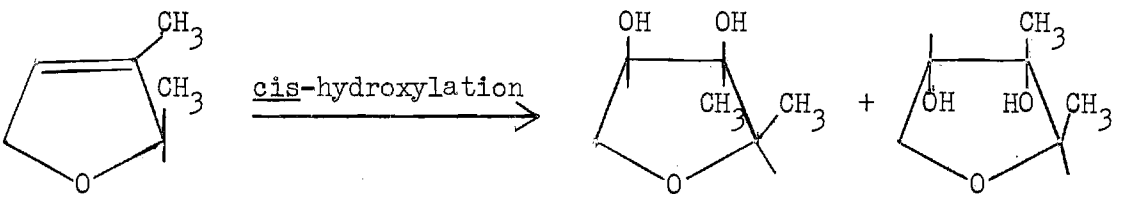


II

The final reaction in the proposed synthetic sequence was the cis-hydroxylation of 2,3-dimethyl-2,5-dihydrofuran (III). The products of this reaction would be expected to be dl-dihydrodideoxystreptose and dl-4-epidihydrodideoxystreptose (IV). 2,5-Dihydrofurans are ordinarily



III II IV

synthesized by cyclization of the corresponding cis-2-butene-1,4-diols. These diols are frequently obtained from 2,5-dimethoxy-2,5-dihydrofurans by hydrolysis and reduction; the 2,5-dimethoxy-2,5-dihydrofurans are usually obtained by oxidation of the corresponding furans in methanol. Thus the synthesis of dl-dihydrodideoxystreptose required, initially, a synthesis of 2,3-dimethylfuran. Since this compound is not readily available, compounds derived from furan and 2-methylfuran served as useful model compounds for the various reactions that were used for the conversion of 2,3-dimethylfuran to dl-dihydrodideoxystreptose.

2,3-Dimethylfuran was synthesized in four steps from chloroacetaldehyde and ethyl acetoacetate; an overall yield of 36% was obtained. This synthesis is distinctly superior to those reported in the literature since fewer steps were required and a better overall yield resulted. 2-Methylfuran and 2,3-dimethylfuran were converted into the corresponding 2,5-dimethoxy-2,5-dihydro- compounds by oxidation with bromine in methanol at -40° in yields of 70% and 84%, respectively.

Acid catalyzed hydrolysis of 2,5-dimethoxy-2,5-dihydro-2-methylfuran did not produce the anticipated 4-oxo-cis-2-pentenal. The product that was obtained was reduced with sodium borohydride and then heated with Dowex 50W-X8 ion-exchange resin. The mixture of substances that resulted

could not be resolved into the pure compounds, and structural formulas for the compounds could not be determined.

2,5-Dimethoxy-2,5-dihydro-2-methylfuran and 2,5-dimethoxy-2,5-dihydro-2,3-dimethylfuran were hydrolyzed using distilled water, and gave 4-oxo-cis-2-pentenal and 3-methyl-4-oxo-cis-2-pentenal, respectively, in good yield. These dicarbonyl compounds were converted to the corresponding diols by reduction with sodium borohydride.

The reported conditions for the conversion of cis-2-butene-1,4-diol into 2,5-dihydrofuran were reproduced. When these same conditions were used with cis-2-pentene-1,4-diol, trans-2-pentenal, an allylic rearrangement product, was the only product observed.

The cis-alkene diols were converted into the corresponding 2,5-dihydrofurans by the following reaction sequence: bromination, cyclization by heating with Dowex 50W-X8 ion-exchange resin, which gave the respective 3,4-dibromotetrahydrofurans, and debromination by heating with zinc dust. The overall yields of 2,5-dihydrofuran, 2,5-dihydro-2-methylfuran, and 2,5-dihydro-2,3-dimethylfuran from the corresponding cis-alkene diols were 58%, 37%, and 26%, respectively. 2,5-Dihydro-2,3-dimethylfuran was also synthesized from acetoin and vinyltriphenyl phosphonium bromide in 42% yield using the literature procedure.

Using the three 2,5-dihydrofurans, various cis-hydroxylation procedures were investigated. Hydroxylation of 2,5-dihydrofuran using the osmium tetroxide reagent gave a poor yield of meso-3,4-dihydroxytetrahydrofuran. Hydroxylation of 2,5-dihydro-2,3-dimethylfuran using the same reagent gave only a 2.8% yield of diols. dl-4-Epidihydrodideoxystreptose and dl-dihydrodideoxystreptose were produced in a ratio of 3.7:1 in this

reaction. The silver acetate-iodine-wet acetic acid reagent gave good yields of diols from 2,5-dihydrofuran and 2,5-dihydro-2-methylfuran; from the latter compound, predominantly dl-3-nordihydrodideoxystreptose was obtained. Hydroxylation of 2,5-dihydro-2,3-dimethylfuran using the silver acetate-iodine-wet acetic acid reagent gave only dl-4-epidihydrodideoxystreptose in poor yield. Good yields of diols were obtained from all three 2,5-dihydrofurans using aqueous potassium permanganate. From 2,5-dihydro-2,3-dimethylfuran this reagent produced dl-4-epidihydrodideoxystreptose and dl-dihydrodideoxystreptose in a ratio of 3.4:1.

The epimeric diols from cis-hydroxylation of 2,5-dihydro-2-methylfuran could not be separated by gas-liquid chromatography. The epimeric diols resulting from cis-hydroxylation of 2,5-dihydro-2,3-dimethylfuran, dl-4-epidihydrodideoxystreptose and dl-dihydrodideoxystreptose, could be separated by gas-liquid chromatography and by fractional crystallization. The diol produced in smaller amount from potassium permanganate hydroxylation of 2,5-dihydro-2,3-dimethylfuran had gas-liquid chromatographic behavior and infrared and nuclear magnetic resonance spectra that were identical with those obtained using a sample of authentic L-dihydrodideoxystreptose. Thus the hydroxyl groups at C_2 and C_3 of L-dihydrodideoxystreptose, as well as those in L-streptose, are cis and the structures are correct as assigned.

A partial optical resolution of dl-3-nordihydrodideoxystreptose, by fractional crystallization of the brucine salt of the phthalate derivative, was effected. Numerous attempts to effect an optical resolution of dl-dihydrodideoxystreptose were unsuccessful.

The compounds resulting from this research have been thoroughly

characterized, especially by nuclear magnetic resonance spectroscopy. Analyses of the nuclear magnetic resonance spectra of dl-dihydrodideoxystreptose, dl-4-epidihydrodideoxystreptose, and a number of their derivatives have enabled an estimate of the conformation of these molecules in solution to be determined.

CHAPTER I

INTRODUCTION

Streptomycin

Streptomycin was first isolated in 1944 by Waksman and co-workers from cultures of Streptomyces griseus, an organism of the order Actinomycetales (1). Unlike streptothricin (2), an antibiotic obtained from the cultures of a related organism, streptomycin was found to have low toxicity, and consequently its pharmacology and production have been extensively studied (2). The substance was found to be both strongly bacteriostatic and bacteriocidal against a wide variety of microorganisms and was the first drug proved to be effective against tuberculosis. The antibiotic has also been used effectively in the treatment of many other diseases such as leprosy, tularemia, typhoid fever, and brucellosis (2,3). In recent years, streptomycin and related antibiotics have been second in importance only to the penicillins (2). The medical aspects (2) and early development (4) of streptomycin have been reviewed.

Streptomycin was shown to be a water-soluble, levorotatory, basic compound that was sensitive to acids and bases (1). Considerable difficulty was experienced in the purification of salts of streptomycin because of their high molecular weights. The molecular formula of streptomycin salts (2) was finally established to be $C_{21}H_{39}N_7O_{12} \cdot 3\ HX$.

Structure of Streptomycin

Reduction of streptomycin trihydrochloride using platinum and

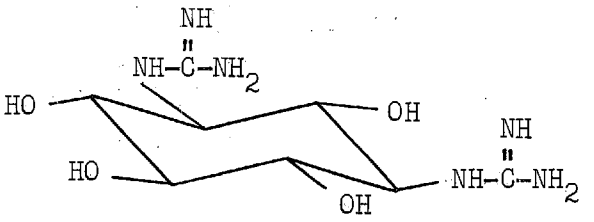
hydrogen at atmospheric pressure resulted in the absorption of one molar equivalent of hydrogen and the formation of a material that was named dihydrostreptomycin trihydrochloride (2). The antibiotic activity and toxicity exhibited by dihydrostreptomycin differed only slightly from that of streptomycin. This is an extremely rare occurrence, since any structural change in an antibiotic usually results in a marked decrease or total loss of activity (2,5). Dihydrostreptomycin has since been shown to be a major fermentation product in the cultures of Streptomyces humidus (6). Because streptomycin formed oxime and semicarbazone derivatives, and dihydrostreptomycin failed to be inactivated by carbonyl reagents that inactivated streptomycin, a free or potentially free carbonyl group was inferred to be present in streptomycin.

Streptomycin gave a positive Sakaguchi test (9), which indicated the presence of a guanidino function. Potentiometric titrations showed that two guanidino groups were present (95). Kuhn-Roth determinations indicated the presence of one C-methyl group (10).

When streptomycin was treated with methanolic hydrogen chloride, two major products resulted. The fragment of molecular formula $C_8H_{18}N_6O_4$ (isolated as its dihydrochloride salt) was named streptidine (I), and the fragment of molecular formula $C_{13}H_{22}NO_7(OCH_3)_3$ (isolated as its hydrochloride salt) was named methyl streptobiosaminide dimethyl acetal (II) (7,8).

$$\text{Streptomycin } C_{21}H_{39}N_7O_{12}\cdot 3HCl \xrightarrow[CH_3OH]{HCl} C_8H_{18}N_6O_4\cdot 2HCl \text{ (I)} + C_{13}H_{22}NO_7(OCH_3)_3\cdot HCl \text{ (II)}$$

Streptidine (I) was shown to be the optically inactive 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane isomer that has all the groups equatorial (2,11,12,13). The structure of streptidine has been confirmed by



I

synthesis (13) and the absolute stereochemistry of the carbon atoms of streptidine in streptomycin has been determined (14).

Mineral acid hydrolysis of streptomycin furnished, in addition to streptidine (I), amorphous streptobiosamine hydrochloride (III), ($C_{13}H_{23}NO_9 \cdot HCl$) (15).

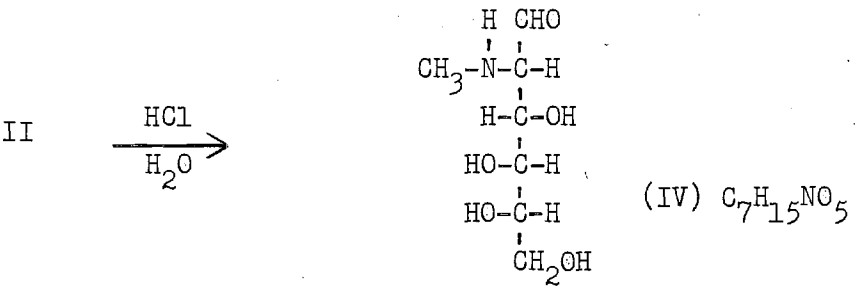
$$C_{21}H_{39}N_7O_{12} \cdot 3HX \xrightarrow[HCl]{H_2O} C_8H_{18}N_6O_4 \cdot 2HCl \text{ (I)} + C_{13}H_{23}NO_9 \cdot HCl \text{ (III)}$$

Streptomycin

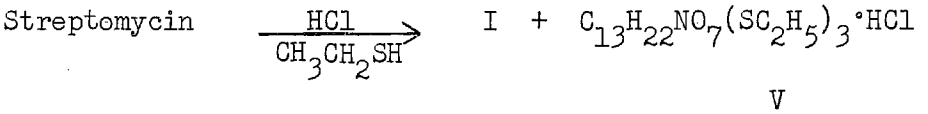
Based on the observations that streptidine does not contain a carbonyl group, and that the other methanolysis product of streptomycin contains three more carbon atoms than streptobiosamine (III), the second fragment obtained in the aqueous hydrolysis of streptomycin, it was concluded that the carbonyl group of streptomycin resides in the streptobiosamine portion of the molecule. It was apparent that the carbonyl group of streptomycin was converted to the dimethyl acetal during

methanolysis; the presence of the third methyl group in the streptobiosamine fragment indicated that streptidine was joined glycosidically to streptobiosamine. It has been shown that streptidine is joined to streptobiosamine through the C_4 hydroxyl group of streptidine (16).

Treatment of II with aqueous acid, followed by acetylation, yielded a compound of molecular formula $C_{17}H_{25}NO_5$. This formula was satisfactory for a pentaacetyl-N-methylhexosamine (17). Chemical and physical data obtained for this compound, and certain derivatives of it, indicated that the nitrogen-containing fragment resulting from this hydrolysis was N-methyl-L-glucosamine (IV). The structure of this portion of the streptomycin molecule was confirmed by synthesis (17).



When streptomycin was treated with ethanethiol and hydrogen chloride, streptidine (I) and ethyl thiostreptobiosaminide diethyl dithioacetal (V) were produced (18). Acetylation of V furnished two crystal-



line anomers that gave the same product, tetraacetyldihydrodideoxystreptobiosamine (VI) ($C_{21}H_{33}NO_{11}$), after desulfurization of V with Raney nickel and reacetylation (10,19). Since N-acetyldihydrodideoxystrepto-

biosamine (VII) ($C_{14}H_{28}NO_8$), produced by partial deacetylation of VI, gave no reducing tests (16), and mineral acid hydrolysis of it furnished N-methyl-L-glucosamine it was concluded that the N-methyl-L-glucosamine portion of the streptomycin molecule was joined glycosidically to the other component of the streptobiosamine fragment (16). This component was named streptose (VIII) (16).

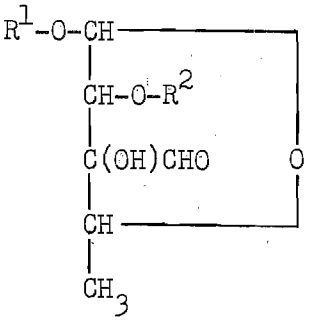
Oxidation of streptomycin trihydrochloride using bromine water gave an acid which was named streptomycinic acid. This compound contained the same number of carbon atoms as streptomycin. This acid yielded, upon methanolysis, streptidine (I) and a substance that contained two O-methyl groups. Since the substance showed absorption in the infrared region at 5.77 μ (5) (characteristic of an ester carbonyl group), and since alkaline hydrolysis removed only one of the O-methyl groups, it was concluded that the free (or potentially free) carbonyl group of streptomycin was aldehydic in nature.

Streptidine and N-methyl-L-glucosamine have been shown to be glycosidically joined to streptose and therefore cannot have the free (or potentially free) carbonyl group in the streptomycin molecule. From this observation it was concluded that the aldehyde group in streptomycin resides in the streptose portion of streptomycin.

From an examination of the molecular formulas of streptomycin, streptidine, and N-methyl-L-glucosamine, it was evident that streptose has the molecular formula $C_6H_{10}O_5$ (16).

$C_{21}H_{39}N_7O_{12}$	Streptomycin
$-C_8H_{18}N_6O_4$	Streptidine
$-C_7H_{15}NO_5$	N-Methyl-L-glucosamine
$+ \quad H_4 \quad O_2$	Two moles of water
$C_6H_{10}O_5$	Streptose

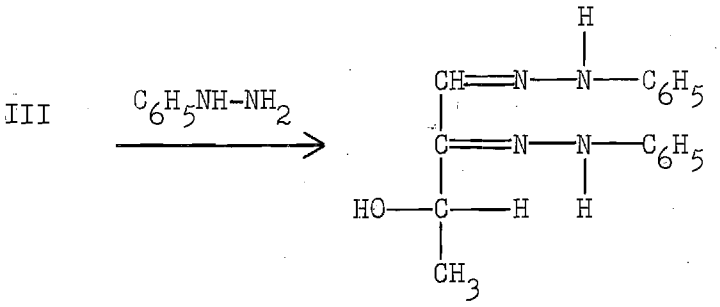
Although streptose has never been isolated as a degradation product of streptomycin, the structure of streptose in streptomycin has been determined from the physical and chemical data obtained from certain degradation products of streptose and streptomycin (97). The structure of streptose in streptomycin and selected data pertinent to the determination of this structure are given below.



R^1 = Streptidinyl

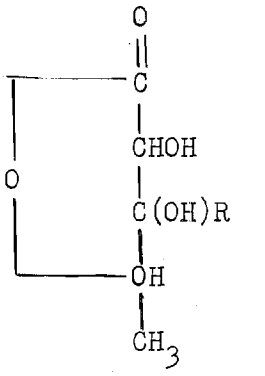
R^2 = N-Methyl-L-glucosaminyl

Amorphous streptobiosamine hydrochloride (III), yielded 4-deoxy-L-erythrose phenylosazone upon treatment with excess phenylhydrazine. The structure of this product was proved by synthesis (15). This result



established the L absolute configuration at C_4 in streptose.

Treatment of the tetraacetate of ethyl thiostreptobiosaminide diethyl dithioacetal (V) with mercuric chloride solution gave crystalline tetraacetylstreptobiosamine (20), which was oxidized with bromine water. After reacetylation, pentaacetylstreptobiosamic acid monolactone (IX) ($C_{23}H_{31}NO_5$) was obtained (20). This compound gave, upon acid hydrolysis, N-methyl-L-glucosamine and a new compound, streptosonic acid monolactone (X) ($C_6H_8O_6$), which was obtained in crystalline form and was converted to a dextrorotatory diamide (20). Catalytic reduction of tetraacetylstreptobiosamine, followed by bromine water oxidation and acid hydrolysis of the resulting product, furnished dihydrostreptosonic acid lactone (XI) (20). Dihydrostreptosonic acid lactone was converted into a dextrorotatory hydrazide.



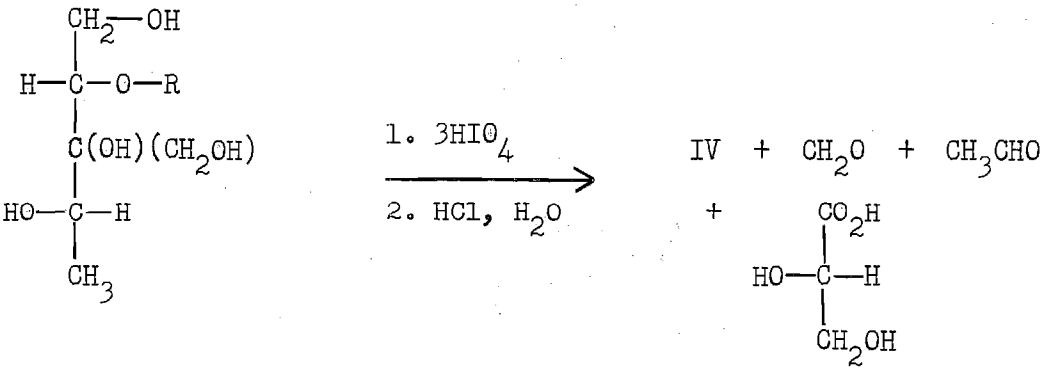
X, R = CO_2H

XI, R = CH_2OH

Application of Hudson's amide and hydrazide rules to the diamide of streptosonic acid monolactone and to the hydrazide of dihydrostreptosonic acid lactone indicated that the absolute configuration at C_2 in streptose was D (21).

Vigorous catalytic hydrogenation transformed N-acetylstreptobiosamine into N-acetyltetrahydrostreptobiosamine (XII). N-Acetyltetrahy-

drostreptobiosamine yielded, after oxidation with periodic acid and subsequent acid hydrolysis of the reaction products, N-methyl-L-glucosamine, acetaldehyde, formaldehyde, and L-glyceric acid (22). This result confirmed the assigned D absolute configuration at C_2 in streptose and showed that the position of attachment of the N-methyl-L-glucosamine fragment to streptose was at C_2.

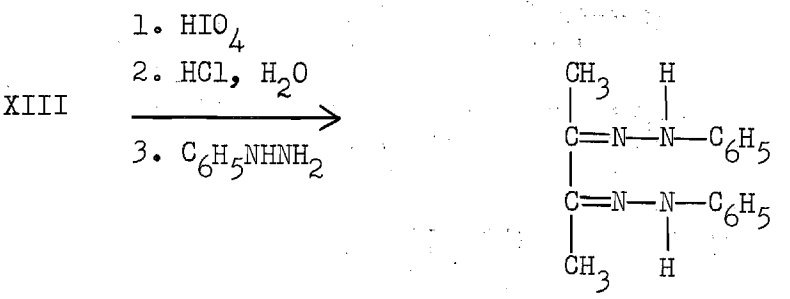


XII

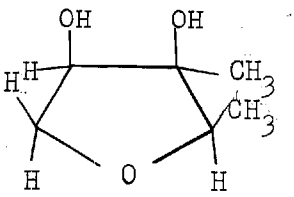
R = N-Acetyl-N-methyl-L-glucosaminyl

When tetraacetyldihydrodideoxystreptobiosamine (VI) was treated with aqueous acid, N-methyl-L-glucosamine (IV), and a new crystalline material, which had the molecular formula $C_6H_{12}O_3$, were obtained. The new substance was named dihydrodideoxystreptose (XIII) and was characterized by a crystalline bis-p-nitrobenzoate derivative (17,19), m.p. 141-142° (23).

Oxidation of dihydrodideoxystreptose with periodic acid, followed by acid hydrolysis, yielded a solution, which when treated with an excess of phenylhydrazine, gave the phenylosazone of biacetyl (17, 19). This result showed that the two terminal methyl groups of dihydrodideoxystreptose were part of a four-carbon fragment that was inert to



the action of periodic acid. Since the compound must contain an α-glycol grouping and an oxygen atom bridge from C_1, the compound must be a 3,4-dihydroxy-2,3-dimethyltetrahydrofuran (96).



XIII

Dihydrodideoxystreptose (XIII) was shown to enhance the conductivity of boric acid solutions (19); this result indicated the cis-arrangement of the α-glycol grouping. Extensive investigations (24,82) have shown that certain cis-α-glycols, notably those that are contained in five-membered rings, cause large increases in the conductivity of boric acid solutions, and that the corresponding trans-α-glycols actually decrease the conductivity of the boric acid solutions. This is presumably caused by the fact that the hydroxyl groups in a cyclic five-membered cis-α-glycol are held in close proximity to each other by the nearly planar ring and can form a cyclic boric acid complex, while the hydroxyl groups of the corresponding trans-compound are held in a position remote from each other and cannot form the cyclic boric acid complex.

Selected data (82) on the enhancement of the conductivities of boric acid solutions by cis-α-glycols with structures similar to dihydrodideoxystreptose are given below.

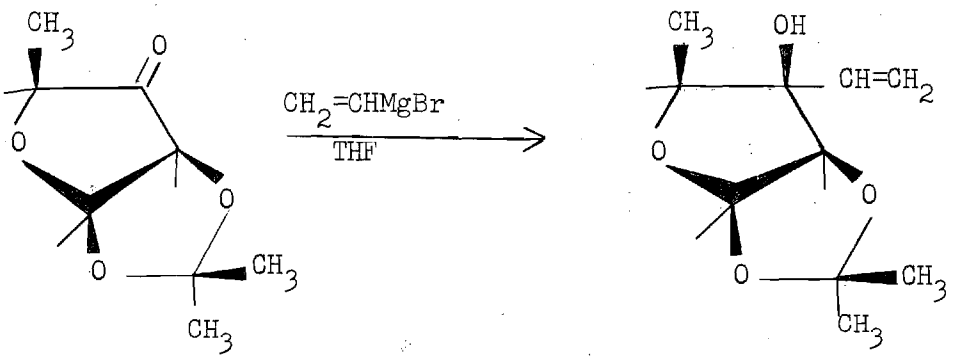
Substance	Conc.	Δ*
cis-Cyclopentane-1,2-diol	0.5 M.	149
trans-Cyclopentane-1,2-diol	0.53 M.	-8
cis-1-Methylcyclopentane-1,2-diol	0.5 M.	114
trans-1-Methylcyclopentane-1,2-diol	0.5 M.	-8
cis-Indane-1,2-diol	0.143 M.	63.2
trans-Indane-1,2-diol	0.05 M.	-0.8

* The increase in conductivity Δ is defined as the conductivity observed for the compound in 0.5 M. boric acid minus the sum of the conductivities of the aqueous solutions of equal concentrations of the polyhydroxy compound and of 0.5 M. boric acid expressed in Kohlrausch-Holborn (26) units multiplied by 10^6.

Since the configuration at C_2 in streptose has been shown to be D, and the α-glycol grouping in dihydrodideoxystreptose was indicated to be cis, the D absolute configuration at C_3 in streptose was assigned (19).

L-Streptose, L-streptosonic acid monolactone, and L-dihydrostreptosonic acid lactone have recently been synthesized (25) from 5-deoxy-L-arabinose by a route which was completely stereospecific for C_2 and C_4. The absolute stereochemistry of the starting 5-deoxy-L-arabinose at C_2 and C_4 was retained in all the intermediates involved in this synthesis. The assigned absolute stereochemistry at C_2 and C_4 in L-streptose and derivatives was therefore confirmed by syntheses. A key intermediate in

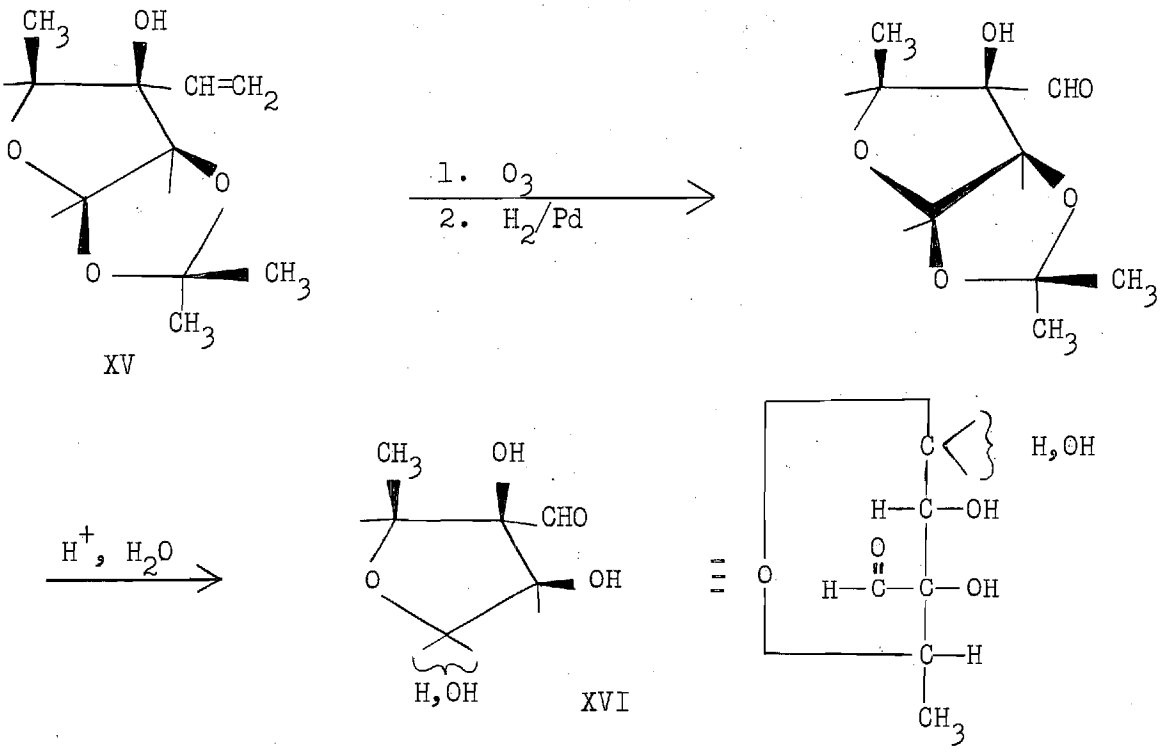
this synthesis was 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (XIV) which gave, upon reaction with vinyl magnesium bromide, only one vinyl carbinol, which was assigned the lyxo configuration (XV).



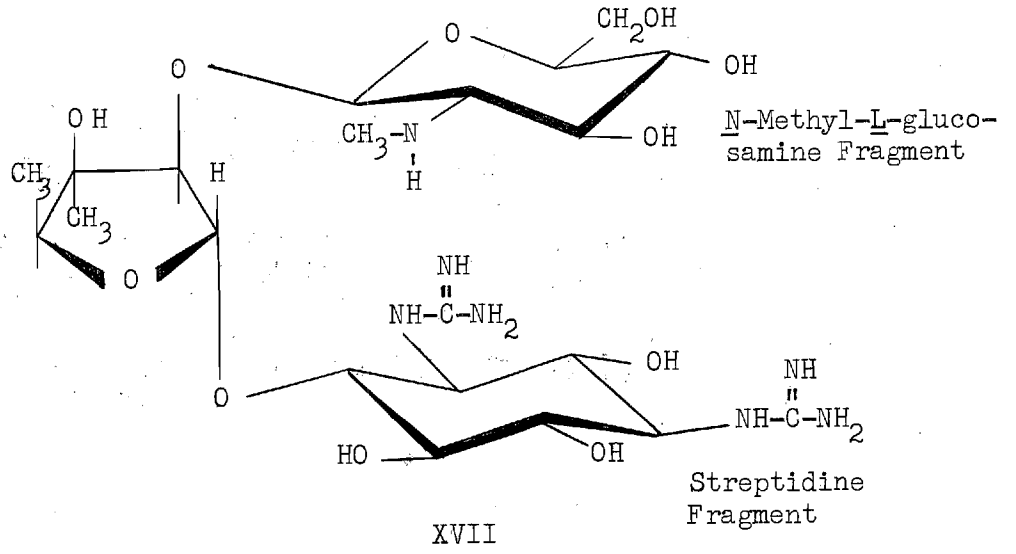
XIV XV

This assignment was made, assuming Grignard addition from the less hindered side of the carbonyl group, after an examination of molecular models indicated that the side of the carbonyl group corresponding to formation of the lyxo isomer was less sterically hindered than the side of the carbonyl group corresponding to the formation of the arabino isomer. Since the product of the Grignard addition to XIV yielded L-streptose (XVI) after ozonolysis, reductive work-up, and removal of the isopropylidene group, the lyxo configuration (D at C_3) for L-streptose was indicated. This result supported, but did not unequivocally prove, the absolute stereochemistry of L-streptose assigned as previously described.

The configuration of the glycosidic linkages in streptomycin have been determined; both the glycosidic bond in streptose (27) and in N-methyl-L-glucosamine (28) have been shown to have the α absolute



configuration. The assigned structure of streptomycin in complete stereochemical detail is represented by XVII.



XVII

Purpose of the Research

The structure and absolute stereochemistry of the carbon atoms of streptidine in streptomycin and structure and absolute stereochemistry of N-methyl-L-glucosamine have been determined and confirmed by synthesis. The gross structure and assigned absolute stereochemistry at C_2 and C_4 in streptose have been confirmed by syntheses, and the absolute stereochemistry at C_3 in streptose has been supported, but not unequivocally proved, by the synthesis of streptose.

The identity of a synthetic sample of dihydrodideoxystreptose, prepared by a route that would insure the cis-orientation of the hydroxyl groups, with a naturally derived specimen would confirm the assigned absolute stereochemistry at C_3 and C_4 in L-dihydrodideoxystreptose. This result would also unequivocally prove the absolute stereochemistry of L-streptose at C_3 and complete the synthetic proof of the absolute stereochemistry of streptomycin with the exception of the glycosidic linkages.

Streptose, except for hydroxystreptose (a component of the relatively minor antibiotic hydroxystreptomycin), is the only naturally occurring branched chain carbohydrate that contains a branch aldehyde function. Since streptomycin is second in importance only to the penicillins and contains the unusual streptose fragment, it would be desirable to complete the synthetic verification of the assigned absolute stereochemistry of streptose.

The purpose of this research was the synthesis of the 3,4-dihydroxy-2,3-dimethyltetrahydrofuran structure (XIII) assigned to dihydrodideoxystreptose by a pathway that would result in the cis-orientation

of the hydroxyl groups, and to show that the synthetic sample was identical with a naturally derived sample.

CHAPTER II

EXPERIMENTAL

Apparatus and Techniques

Anhydrous ether was purchased (Merck reagent 71633) and dried overnight over sodium ribbon before use. Anhydrous pyridine was prepared by repeated distillation of purified pyridine (Matheson, Coleman, and Bell PX2025) from potassium hydroxide until the distillate did not turn yellow upon storage over potassium hydroxide pellets. Anhydrous ethyl acetate was prepared by distillation from phosphorus pentoxide powder. Anhydrous methanol was prepared as described elsewhere (29). Anhydrous dimethylformamide was prepared by distillation from calcium oxide powder. Anhydrous isopropyl ether was prepared by distillation from sodium and was stored over sodium ribbon. Redistilled benzene was dried by storage over sodium ribbon. Dowex 50W-X8 ion-exchange resin (Baker reagent 1930) was purchased (containing 55% water) and was used directly in the hydrogen phase.

Unless otherwise stated, all melting points were determined using a Köfler hot stage and are corrected. Melting points determined in sealed tubes were observed in an oil bath and are corrected.

Microanalyses were performed by Galbraith Laboratories (Knoxville, Tennessee) and Bernhardt Laboratories (Mülheim, West Germany). Optical rotations were determined using a Bellingham and Stanley polarimeter (Model No. 377619) equipped with a General Electric Sodium lab-arc lamp as the source of the sodium D line. The error given indicates the maximum

deviation from the mean value for five measurements. Refractive indices were determined using a Bausch and Lomb Abbé-56 refractometer. Infrared spectra were determined using a Perkin Elmer Model 137 Infracord recording spectrometer.

Unless otherwise stated all evaporations and concentrations were performed using a Rinco (Model VE-1000-A) rotating evaporator at temperatures below 60° using water aspirator vacuum. Drying of solutions and extracts in organic solvents was done by addition of anhydrous magnesium sulfate (Malinckrodt AR 6070) unless otherwise stated; the drying agent was removed by gravity filtration and was washed thoroughly with several portions of the solvent.

Gas-liquid chromatography (GLC) was performed using a Glowall Corp. Chromalab Model A-110 instrument equipped with a Minneapolis Honeywell continuous recorder. The columns employed (dimensions 6 ft. x 4 mm.) were packed with the specified adsorbant on the given support, all of which were purchased from Applied Science Laboratories. The instrument was always equilibrated at the specified temperature and argon inlet pressure before use. Retention times for given peaks were measured from the solvent front (initial recorder response). Peak areas were determined using a Gelman Instruments Co. (Model 39231) planimeter.

Silicic acid chromatography columns were prepared by making a slurry of the indicated amount of silicic acid (100 mesh, Mallinckrodt AR 2847) in chloroform and pouring it into a cylindrical column equipped with a coarse fritted glass disc at the bottom. The excess chloroform was drained and the column packed by vibration until the adsorbant was firm. Aluminia columns were prepared by partly filling a cylindrical

column that had a glass wool plug at the bottom with solvent, and slowly adding the specified amount of acid washed aluminia (Merck reagent 71695). The excess solvent was drained during the addition of the aluminia and vibration was used until the aluminia was firm.

All pH measurements were made using Hydrion paper. Analytical thin-layer chromatography (TLC) plates were spread 0.25 mm. thick using the indicated adsorbant, and preparative thin-layer chromatography plates were spread using the given adsorbant and were 1.0 mm. thick. All material used in thin-layer chromatography was purchased from Brinkman Instruments Co., Westbury, New York.

Nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer. The magnet temperature was essentially constant between 30^0 and 40^0 during the determination of a given spectrum. All chemical shift values are reported in τ units ($\tau = 10-\delta$). Tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) were used as internal standards. The 500 cps. scale width was used for all spectra given as figures. Spin-spin coupling constants (J, measured in cps.) given with more than one significant figure were determined using the 50 cps. scale. Concentrations given for spectra determined in solutions are per cent by weight.

Countercurrent distribution was performed using a two hundred transfer H. O. Post Scientific Instruments Co. Model B-3 countercurrent distribution apparatus.

Spinning band distillation columns used were the lab size Nester-Faust Model NF-135 and the micro Nester-Faust column NF-105.

Exploratory Studies Using Model Compounds from Furan

dl-2,3-Dibromobutane-1,4-diol and dl-3,4-Dibromotetrahydrofuran

A solution of 46.4 g. of bromine (0.29 mole) in 100 ml. of methylene chloride was added dropwise, with stirring, to a mixture of 30.0 g. (0.283 mole) of cis-2-butene-1,4-diol (National Aniline and Film Co.) and 50 ml. of methylene chloride contained in a 250-ml. three-necked round-bottomed flask fitted with a mechanical stirrer, an addition funnel, and a reflux condenser; the mixture was cooled in an ice bath. When the addition was complete, a slight red coloration was present. This was discharged by the addition of several drops of cis-2-butene-1,4-diol. The solvent was evaporated from the tan methylene chloride solution.

To the resulting dl-2,3-dibromobutane-1,4-diol, a dark sirup, which was contained in a 100-ml. round-bottomed flask, 6 g. (0.035 mole) of p-toluenesulfonic acid monohydrate was added. The mixture was heated in an oil bath to 160-165° and distilled under water aspirator vacuum. The temperature of the oil bath was slowly raised to 180°; when no more material distilled, heating was discontinued. The heterogeneous distillate was extracted with 60 ml. of methylene chloride. The organic layer was dried and the methylene chloride was evaporated. The residue was distilled *in vacuo*, and gave 53.84 g. (69%) of dl-3,4-dibromotetrahydrofuran, b.p. 94-96°/24 mm., $\eta_D^{20^\circ}$ = 1.5479 [lit. (30), b.p. 90.5-91.5°/19 mm., $\eta_D^{20^\circ}$ = 1.5490].

The n.m.r. spectrum of the compound (neat) showed absorptions at 5.22-5.58 (4H, complex signal) and 5.68-5.98 τ (2H, complex signal).

dl-3,4-Dibromotetrahydrofuran from 2,5-Dihydrofuran

A solution of 80 g. (0.5 mole) of bromine in 100 ml. of methylene

chloride was added dropwise to a solution of 35.0 g. (0.5 mole) of 2,5-dihydrofuran in 50 ml. of methylene chloride cooled in an ice bath and contained in a 500-ml. round-bottomed flask that had been fitted with a mechanical stirrer, an addition funnel, and a reflux condenser. When the addition was complete, the methylene chloride was evaporated and the residue was distilled *in vacuo*. This gave 97.80 g. (85%) of *dl*-3,4-dibromotetrahydrofuran, b.p. 94-96°/24 mm. [lit. (30), b.p. 90.5-91.5°/19 mm.]. The n.m.r. spectrum of the compound (neat) showed absorptions at 5.22-5.58 (4H, complex signal) and 5.68-5.98 τ (2H, complex signal).

2,5-Dihydrofuran

From *cis*-2-Butene-1,4-diol. A mixture of 50.0 g. (0.568 mole) of *cis*-2-butene-1,4-diol and 10 g. of Dowex 50W-X8 ion-exchange resin in the hydrogen phase was placed in a 100-ml. three-necked flask fitted with a mechanical stirrer and a distillation apparatus. The reaction vessel was placed in an oil bath that had been preheated to 135°; after several minutes, distillation began, and the distillate showed b.p. 65-70°. When no more distillate collected, the reaction was stopped. The distillate was extracted with 40 ml. of pentane. The pentane extract was dried and distilled using a lab-size spinning-band distillation column. After the pentane had been removed, 23.40 g. (59%) of 2,5-dihydrofuran was collected, b.p. 66-68° [lit. (31), b.p. 66-67.5°]. This was followed by 3.21 g. (7.6%) of *trans*-crotonaldehyde, b.p. 99-101° [lit. (31) b.p. 100-102°]. The 2,5-dihydrofuran had an n.m.r. spectrum (neat) identical to that of an authentic sample (Columbia Organic Chemicals Co., Inc., 8-123). The 2,5-dihydrofuran showed adsorptions at 4.10 (2H, complex) and 5.46 τ (4H, complex).

From dl-3,4-Dibromotetrahydrofuran. A mixture of 15.65 g. (0.239 atom) of zinc dust and 15 ml. of isoamyl alcohol was placed in a three-necked flask fitted with a distillation apparatus, a mechanical stirrer, and an addition funnel. The mixture was heated to 110°, and a solution of 27.58 g. (0.12 mole) of dl-3,4-dibromotetrahydrofuran in 25 ml. of isoamyl alcohol was added at a rate that maintained moderate distillation. When the addition was complete the reaction mixture was distilled, and the distillate was collected to 125°. This distillate was distilled on a lab-size spinning-band distillation column and 6.98 g. (84%) of 2,5-dihydrofuran was collected, b.p. 66-68° [lit. (31), b.p. 66-67.5°]. The n.m.r. and IR spectra of this sample were identical with those of an authentic sample. (The overall yield from cis-2-butene-1,4-diol was 58%.)

A mixture of 41 g. (0.63 atom) of zinc dust and 40 ml. of ethylene glycol was placed in a 100-ml. three-necked flask fitted with a mechanical stirrer, a distilling apparatus, and an addition funnel. This mixture was heated to 135° while stirring, and a mixture of 70 g. (0.305 mole) of dl-3,4-dibromotetrahydrofuran in 35 ml. of ethylene glycol was added dropwise at a rate of two drops per second. Distillation of the 2,5-dihydrofuran proceeded during the addition of the dl-3,4-dibromotetrahydrofuran. When the addition was complete, the reaction mixture was heated with a low flame until the temperature of the distillate reached 150°. The entire distillate was then redistilled using a short Vigreux column and 18.10 g. (83%) of 2,5-dihydrofuran was collected, b.p. 66-68° [lit. (31), b.p. 66-67.5°].

The n.m.r. spectrum of the product was identical with that of an authentic sample.

Hydroxylation of 2,5-Dihydrofuran Using Osmium Tetroxide

A mixture of 100 ml. of 30% aqueous hydrogen peroxide and 400 ml. of redistilled t-butyl alcohol was shaken with several small portions (ca. 2 g.) of anhydrous sodium sulfate until two layers separated. The lower layer was removed, and the organic layer was dried first with anhydrous sodium sulfate and finally with anhydrous calcium sulfate. By this method (32) a 6.32% solution of hydrogen peroxide in t-butyl alcohol was obtained.

A mixture of 35.0 g. (0.5 mole) of 2,5-dihydrofuran and 272 ml. (0.5 mole of hydrogen peroxide) of the t-butyl alcohol solution of hydrogen peroxide was placed in a 1-l. flask and cooled to 0°. To this was added 4.91 ml. of a 0.5% solution of osmium tetroxide in t-butyl alcohol, and the resulting mixture allowed to stand at 0° for 12 hr. Zinc dust (ca. 1 g.) was then added, and after 0.5 hr., the solvent was evaporated. Distillation of the residue in vacuo yielded 12.5 g. (24%) of meso-3,4-dihydroxytetrahydrofuran, b.p. 90-91°/0.75 mm. [lit. (33), b.p. 105°/0.5 mm.].

2,5-Dihydrofuran (28.0 g., 0.4 mole), t-butyl alcohol (100 ml.), and distilled water (25 ml.) were placed in a 250-ml. three-necked flask that had been fitted with a mechanical stirrer, an addition funnel, and a reflux condenser. Osmium tetroxide (1.5 mg.) was added; this was followed, while stirring, by the dropwise addition of 45.5 g. (0.401 mole) of 30% aqueous hydrogen peroxide. The reaction mixture was cooled in an ice bath during the addition, and the rate of addition of the hydrogen peroxide solution was regulated so as to maintain a temperature of 40-45°. When the addition was complete, zinc dust (ca. 1 g.) was added and

the solvents were evaporated. Distillation of the residue *in vacuo* yielded 4.0 g. (10.4%) of *meso*-3,4-dihydroxytetrahydrofuran, b.p. 107-110°/2.0 mm. [lit. (33), b.p. 105°/0.5 mm.]. There remained in the distillation flask a large quantity of very dark material that solidified to a black glass upon cooling.

2,5-Dihydrofuran (35 g., 0.5 mole) and osmium tetroxide (3 mg.) were placed in a 250-ml. round-bottomed flask that had been fitted with an alcohol thermometer, a mechanical stirrer, and an addition funnel. The reaction flask was placed in an ice bath, and after the 2,5-dihydrofuran had cooled to 0°, 56.6 g. (0.5 mole) of a 30% aqueous solution of hydrogen peroxide was added dropwise during a period of 3 hr. while stirring. When the addition was complete, the ice bath was removed, and the temperature of the reaction mixture was allowed to slowly increase to 20°. The temperature then rapidly increased to 90°, and the mixture was immediately cooled, while stirring, to 25°. Stirring was continued overnight; the reaction mixture was then allowed to stand three days. The solvent was evaporated and the residue was distilled *in vacuo*. This yielded 11.42 g. (22%) of impure *meso*-3,4-dihydroxytetrahydrofuran, b.p. 100-120°/1.5-2.0 mm. [lit. (33), b.p. 105°/0.5 mm.], which was not investigated further. There remained in the distillation flask *ca.* 15 g. of material that solidified to a dark glass upon cooling.

Hydroxylation of 2,5-Dihydrofuran Using the Silver Acetate-Iodine-Wet Acetic Acid Reagent

A mixture of 35 g. (0.50 mole) of 2,5-dihydrofuran, 2.28 l. of 99.8% glacial acetic acid, and 167.0 g. (1.00 mole) of silver acetate was placed in a 3-l. three-necked flask which had been fitted with a

mechanical stirrer, a reflux condenser, and a powder funnel. Finely powdered iodine (133.0 g., 0.524 mole) was then added over a period of 30 min. while the mixture was stirred at room temperature. When the addition was complete, 225 ml. of aqueous acetic acid (0.5 mole of water, prepared by dilution of 20 ml. of water to 500 ml. with glacial acetic acid) was added and the mixture was heated, while stirring, to 80° for 4.0 hr. The mixture was then allowed to stand at room temperature for 10.0 hr. Solid sodium chloride (15.0 g., 0.257 mole) was then added; after the mixture was stirred for 1.0 hr., it was filtered using suction. The precipitate was washed thoroughly with hot benzene. The filtrate and benzene washings were combined and the solvents were evaporated. The residue was dissolved in 75 ml. of methanol, filtered, and the filtrate was neutralized with 10% methanolic potassium hydroxide. A solution of 35.08 g. (0.624 mole) of potassium hydroxide in the minimum amount of methanol was added and the mixture was allowed to stand 24 hr. The excess potassium hydroxide was then neutralized with 5% aqueous hydrochloric acid at 0°, and most of the methanol was evaporated. The black aqueous solution was extracted continuously with methylene chloride for 48 hr. The methylene chloride extract was dried and the solvent was evaporated. Distillation in vacuo yielded 34.5 g. (68%) of meso-3,4-dihydroxytetrahydrofuran, b.p. 91°/0.75 mm., $\eta_D^{25^\circ}$ 1.4785 [lit. (33), b.p. 105°/0.5 mm., $\eta_D^{20^\circ}$ 1.4800]. The n.m.r. spectrum (40% in chloroform) of the compound showed absorptions at 5.23 (2H, singlet) and 5.57-6.42 τ (6H, complex).

Hydroxylation of 2,5-Dihydrofuran Using Aqueous Potassium Permanganate

A mixture of 35.0 g. (0.5 mole) of 2,5-dihydrofuran and 600 ml. of

distilled water was placed in a 3-l. three-necked flask fitted with a mechanical stirrer, an alcohol thermometer, and an addition funnel. The mixture was cooled in an ice-acetone bath to a temperature of $3^{\circ} \pm 1^{\circ}$, which was maintained throughout the reaction. A solution of 80 g. (0.506 mole) of potassium permanganate in 1.5 l. of distilled water was added at the rate of 25 ml./min., while stirring vigorously. When the addition was complete, the mixture was removed from the ice-acetone bath and allowed to stand 2.0 hr. at room temperature. It was then heated on the steam bath for 1.0 hr., filtered hot using suction, and the precipitate was washed thoroughly with three 200-ml. portions of hot water. The combined aqueous solutions were concentrated to 200 ml. and extracted continuously for 48 hr. with chloroform. This extraction yielded 10.0 g. of material after evaporation of the solvent. The aqueous solution was concentrated to about 150 ml. and solid potassium carbonate was added until the aqueous solution was just slightly less dense than chloroform. The resulting aqueous solution was extracted continuously (three days) with chloroform until no more material was extracted after 24 hr. The residues from all extractions were combined and distilled in vacuo. This yielded 24.75 g. (47.6%) of meso-3,4-dihydroxytetrahydrofuran, b.p. 95-96°/1 mm., $\eta_D^{22^{\circ}}$ 1.4792 [lit. (33), b.p. 105°/0.5 mm., $\eta_D^{20^{\circ}}$ 1.4800]. The n.m.r. and IR spectra of the compound were identical with those of an authentic sample.

meso-3,4-Dibenzoyloxytetrahydrofuran. A solution of 1.01 g. (9.7 mmole) of meso-3,4-dihydroxytetrahydrofuran in 20 ml. of dry pyridine was placed in a 50-ml. Erlenmeyer flask and 4.00 g. (27.9 mmole) of benzoyl chloride was added dropwise, while the mixture was stirred

magnetically. When the addition was complete the mixture was heated on a steam bath for 1.0 hr. The mixture was then cooled and water (50 ml.) was added; this was followed by the addition of solid sodium bicarbonate until the evolution of carbon dioxide ceased. After standing 1.0 hr., the mixture was extracted with three 50-ml. portions of chloroform. The combined chloroform extract was extracted with 1% hydrochloric acid until the chloroform no longer smelled of pyridine. The chloroform extract was then extracted with two 50-ml. portions of water, dried, and the solvent was evaporated; this yielded 2.83 g. (90.5%) of meso-3,4-dibenzoyloxytetrahydrofuran, m.p. 63-66°. An analytical sample was prepared by recrystallizing the crude product five times from methanol and showed m.p. 67°.

Anal.	$C_{18}H_{16}O_5$	Calc'd: C, 69.22; H, 5.16
	(312.3)	Found : C, 69.04; H, 5.13

The n.m.r. spectrum (40%, carbon tetrachloride) of the compound showed absorptions at 1.92-2.38 (4H, complex), 2.38-3.00 (6H, complex), 4.18-4.59 (2H, complex), and 5.60-6.20 τ (4H, complex). The infrared spectrum showed λ_{max} 3.27, 3.44, 5.79, 6.23, 6.88, 7.85, 8.87, 9.77, and 14.14 μ, among others.

Exploratory Studies Using Model Compounds From 2-Methylfuran

Reduction of Ethyl 2-Furoate

Two grams of 10% palladium on carbon was equilibrated by stirring with hydrogen at 32° and 747.0 mm. in 95% ethanol in a quantitative hydrogenation apparatus. When the equilibration was complete, 2.1859 g. (15.59 mmole) of ethyl 2-furoate was added and the hydrogenation was

begun. During an hour, 718.5 ml. (32.08 mmole) of hydrogen was absorbed and then absorption ceased. The catalyst was filtered and the solvent was evaporated. The infrared spectrum (film) of the resulting oil showed λ_{max} 3.32, 3.42, 5.73, 7.31, 7.86, 8.36, 9.20, and 10.80 μ, among others.

One gram of 5% palladium on barium sulfate was equilibrated with hydrogen at 30° and 738.2 mm. in 95% ethanol in a quantitative hydrogenation apparatus. When the equilibration was complete, 1.0158 g. (7.15 mmole) of ethyl 2-furoate was added and the reduction was begun. During 2.3 hrs., 329.0 ml. (14.65 mmole) of hydrogen was absorbed and then absorption ceased. The reaction mixture was not investigated further.

Reduction of 2-Furfuryl Alcohol

One gram of 5% palladium on carbon was equilibrated with hydrogen at 731.1 mm. and 25° in ethanol in a quantitative hydrogenation apparatus. When the equilibration was complete, 1.0599 g. (10.81 mmole) of freshly distilled 2-furfuryl alcohol was added and the reduction begun. In an hour, 453 ml. (20.2 mmole) of hydrogen had been adsorbed and adsorption then stopped. The catalyst was filtered and the solvent was evaporated. The infrared spectrum (film) of the resulting oil was identical with that of an authentic sample of dl-tetrahydro-2-furfuryl alcohol and showed λ_{max} 2.64, 3.24, 3.32, 9.30, 9.50, and 10.79 μ, among others.

Attempted Preparation of 2-Furfuryl-p-toluenesulfonate

To a solution of 10.79 g. (0.11 mole) of freshly distilled 2-furfuryl alcohol, 7.91 g. (0.10 mole) of dry pyridine, and 50 ml. of chloroform, which had been cooled to -15°, a solution of 19.05 g. (0.10 mole) of p-toluenesulfonyl chloride in 75 ml. of chloroform was added dropwise

while the mixture was stirred magnetically. The addition was carried out using an addition funnel fitted with a drying tube. The mixture was allowed to stand overnight at -15°. The solution was then extracted with two 100-ml. portions of ice-cold 1 N hydrochloric acid and then with two 100-ml. portions of saturated sodium bicarbonate solution. The organic layer was dried and the solvent was evaporated at 38°. After removal of the solvent a tan viscous syrup was obtained that developed a dark green color in about twenty minutes. After two hours the preparation had become a viscous black tar, which was discarded.

cis- and trans-2,5-Dimethoxy-2,5-dihydro-2-methylfuran

To 750 ml. of absolute methanol contained in a 2-l. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, a drying tube, and an addition funnel was placed 120 g. (1.225 mole) of anhydrous potassium acetate and 49.5 g. (0.603 mole) of redistilled 2-methylfuran. The mixture was placed in a dry ice-acetone bath and a solution of 96.3 g. (0.603 mole) of bromine in 600 ml. of absolute methanol was added during a period of 30 min. The temperature of the reaction mixture was kept below -30°. When the addition was complete, the mixture was removed from the dry ice-acetone bath and stirred for an additional 15 min. The mixture was then poured into 2.0 l. of saturated calcium chloride solution, and after mixing completely, the solution was extracted with five 250-ml. portions of ether. The combined ether extract was washed with a 300-ml. portion of saturated potassium carbonate solution and was then dried. The ether was removed by distillation through a packed column at atmospheric pressure until the temperature of the distilling vapor reached 75°. The remaining solution, which had a volume

of about 100 ml., was distilled in vacuo. This gave 60.50 g. (70%) of a mixture of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran, b.p. 49-51°/14 mm. $\eta_D^{25°}$ 1.4285 [lit. (34), b.p. 47-49°/11 mm. $\eta_D^{25°}$ 1.4290]. The n.m.r. spectrum (neat) of the preparation showed absorptions for the major component (64%) at 3.82-4.16 (2H, complex), 4.52 (1H, complex), 6.59 (3H, singlet), 6.91 (3H, singlet), and 8.60 τ (3H, singlet). Absorptions for the minor component (36%) were present at 3.82-4.16 (2H, complex), 4.24 (1H, complex), 6.66 (3H, singlet, 6.95 (3H, singlet), and 8.53 τ (3H, singlet). The infrared spectrum of the preparation showed λ_{max} 3.40, 6.12, 7.31, 7.58, 8.15, 8.61, 9.11, 9.31, 9.59, 11.00, and 11.40 μ, among others.

The above procedure is a modification of that of Clauson-Kaas and Limborg (35) who added the methanolic solution of bromine at -7° and obtained the mixture of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran in 65% yield.

The mixture (b.p. 49-51°/14 mm.) was carefully redistilled on a lab-size spinning-band column and the n.m.r. spectrum (neat) of the fraction that had b.p. 50-50.5°/14 mm. showed that partial separation of the mixture of cis and trans isomers had been accomplished. The major component of the original mixture amounted to 85% of the fraction of b.p. 50-50.5°/14 mm.

Attempted Conversion of cis- and trans-2,5-Dimethoxy-2,5-dihydro-2-methylfuran to 2,5-Dihydro-2-methylfuran

Hydrolysis. A mixture of 21.2 g. (0.147 mole) of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran and 17.0 ml. of 0.01 N sulfuric acid was placed in a 100-ml. round-bottomed flask that had been fitted

with a reflux condenser. The mixture was heated to boiling during 5 min., using a low flame, and was then immediately cooled to 25° using an ice bath. Seventeen milliliters of a saturated solution of calcium chloride was then added and the mixture was extracted with three 100-ml. portions of ether. The combined ether extract was dried using calcium chloride and the ether was removed by distillation at atmospheric pressure. Distillation of the residue *in vacuo* yielded a fraction that had b.p. 78-81°/10 mm., which weighed 3.62 g. This was followed by a second fraction, b.p. 81-84°/10 mm., which weighed 9.85 g. [lit. (35), 4-oxo-*cis*-2-pentenal, b.p. 126°/10 mm.]. A considerable quantity of dark red high-boiling material remained, which was not investigated further. The n.m.r. spectra (neat) of both fractions were determined and showed that no appreciable amount of 4-oxo-*cis*-2-pentenal was present in either fraction. The n.m.r. spectrum (neat) of the fraction, b.p. 78-81°/10 mm. showed absorptions at -0.02-0.22 (two doublets), 3.00-3.20 (complex), 5.83-6.30 (complex), 6.38 (singlet), 6.49-6.82 (complex), 7.00-8.32 (complex), 7.59 (singlet), 7.87 (singlet), and 8.50-9.08 τ (complex). The n.m.r. spectrum (neat) of the fraction, b.p. 81-84°/10 mm., showed absorptions at essentially the same positions but with slightly different signal patterns as those of the fraction of b.p. 78-81°/10 mm. The infrared spectra (film) of both fractions were very nearly identical and showed λ_{max} 3.30, 5.73, 5.79, 5.89, 6.95, 8.63, and 10.17 μ, among others. The lower boiling fraction also showed λ_{max} 9.00 and 9.79 μ. There was no corresponding absorption in the spectrum of the higher boiling fraction.

Reduction. A mixture of 62.00 g. (0.43 mole) of *cis*- and *trans*-2,5-dimethoxy-2,5-dihydro-2-methylfuran and 44.0 ml. of 0.01 N sulfuric acid

was heated on the steam bath for 10 min., cooled to 25°, and neutralized with solid sodium bicarbonate. The resulting dark red solution was added dropwise, while stirring and cooling, to a solution of 34.7 g. (0.64 mole) of potassium borohydride in 250 ml. of distilled water. When the addition was complete, the mixture was allowed to stand 3 hr. and the pH of the solution was then adjusted to 4.0 with 5% hydrochloric acid. Solid sodium bicarbonate was then added until the pH of the solution was 6.0. The resulting solution was extracted continuously with methylene chloride for three days. The methylene chloride extract was dried and the solvent was evaporated. The residue was distilled *in vacuo*; this yielded 23.0 g. of material that showed b.p. 124-130°/15 mm., [lit. (36), b.p. 126°/15 mm.].

The n.m.r. spectrum (15%, deuterium oxide) of the preparation showed adsorptions at 5.31 (4 squares, singlet, HOD), 5.75-6.47 (5.8 squares, complex), 6.47-6.69 (9.5 squares, three strong lines), 8.11-8.86 (4.4 squares, broad quartet), 8.82 (doublet, J = 6.5), and 8.85 τ (doublet, J = 6.0) (7.1 squares for the two doublets). The infrared spectrum (film) showed λ_{max} 2.93, 3.36, 6.89, 7.33, 10.61, and 12.53 μ, among others.

Cyclization. A mixture of 73.0 g. of the above preparation and 12.0 g. of Dowex 50W-X8 ion-exchange resin were placed in a 250-ml. three-necked flask that had been fitted with a mechanical stirrer and vacuum distillation apparatus. The flask was placed in a sand bath, and three receivers, which were cooled in a dry ice-acetone bath, were placed in series. The sand bath was heated to 150-160°; distillation began at this temperature and the volatile products of the reaction were distilled from the reaction mixture under water aspirator vacuum. The reaction was complete in 1 hr., and it was found that all the volatile products had

collected in the first trap. The material in the first trap was brought to room temperature and pentane (100 ml.) was added. The lower phase, which separated, was extracted with three 25-ml. portions of pentane. The combined pentane extracts were dried and the solution was distilled, using a lab-size spinning-band column. After removal of the pentane a fraction (42.08 g.) was collected that showed b.p. 133-136°, $\eta_D^{24^\circ}$ 1.4208; this was followed by a second fraction (4.0 g.) that showed b.p. 136-139°. The n.m.r. spectra of the two fractions were identical and showed adsorptions at 5.79-6.59 (11 squares, complex), 6.75-6.80 (9 squares, two singlets), 7.86 (3 squares, asymmetric sextet, $\underline{J}$ = 6.6), 8.36-8.67 (2 squares, complex), 8.80 (4.2 squares, doublet, $\underline{J}$ = 6.0), and 8.85 τ (5.5 squares, doublet, $\underline{J}$ = 6.0). The infrared spectrum (film) of the preparation showed λ_{max} 3.39, 5.88 (weak), 6.84, 7.23, 8.08, 8.40, 9.13, 10.53, 11.18, and 11.97 μ, among others. A portion of the fraction that showed b.p. 133-136° was redistilled, using a micro spinning-band column for elemental analysis. The analytical samples showed b.p. 133° and were taken from adjacent fractions.

<u>Anal.</u>	$C_6H_{12}O_2$	Calc'd:	C, 62.05; H, 10.40
	(116.2)	Found :	C, 62.66; H, 10.00
			C, 63.18; H, 11.47

The remainder of the material was redistilled through a lab-size spinning-band column; a reflux ratio of approximately 100:1 was used. The boiling range observed was 128-133°. Eleven fractions of approximately 1 ml. each were taken. The n.m.r. spectra of fractions 2 and 11 were recorded. The n.m.r. spectra were virtually identical and differed only in the 8.7-8.9 τ region. The intensities of the multiplets in this

region indicated that fraction 2 consisted of approximately 63% of that isomer having the methyl group doublet at highest field, whereas fraction 10 consisted of approximately 51% of this isomer. The boiling points observed for fractions 3, 6, and 11 were 130-131°, 131-131.5°, and 133°, respectively. Analytical results were obtained on these fractions.

Anal.	$C_6H_{12}O_2$	Calc'd:	C, 62.04; H, 10.41
	(116.2)	Found :	C, 61.31; H, 10.18 Fraction 3
			C, 61.24; H, 10.37 Fraction 6
			C, 61.37; H, 10.36 Fraction 11

Separation of the two isomers was also attempted using preparative G.L.C. (30% SE-30). Only one symmetrical peak was observed.

The infrared spectra (film) of the three fractions were identical except for the region 5.00-6.00 μ. Fractions 3 and 6 showed weak absorptions at 5.66, 5.80, and 5.90 μ. Fraction 11 showed no absorption in the region 5.00-6.00 μ, but showed absorptions at 3.39, 6.90, 7.25, 8.10, 8.40, 9.10, 10.50, and 11.94 μ, among others. Fractions 3 and 6 gave immediate orange precipitates when treated with 2,4-dinitrophenylhydrazine reagent but fraction 11 gave no precipitate after standing two days.

Attempted Hydroxylation of cis- and trans-2,5-Dimethoxy-2,5-dihydro-2-methylfuran Using the Silver Acetate-Iodine-Wet Acetic Acid Reagent

A mixture of 10 g. (0.076 mole) of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran, 26.12 g. (0.157 mole) of silver acetate, and 317 ml. of glacial acetic acid was placed in a 500-ml. three-necked flask that had been fitted with a mechanical stirrer, a reflux condenser, a drying tube, and a powder funnel. Finely powdered iodine (18.5 g., 0.073 mole) was then added over a period of 0.5 hr.; stirring was continued for an additional hour, and then 31.3 ml. (0.071 mole of

water) of an aqueous solution of acetic acid (prepared by dilution of 2.00 ml. of distilled water to 50 ml. with glacial acetic acid) was added. The mixture was then heated at 90-95° for 3 hr. while stirring vigorously. The mixture was cooled, treated with solid sodium chloride (ca. 20 g.), and stirred for one hour. The precipitate was filtered and washed thoroughly with two 50-ml. portions of water. The solvent was evaporated from the combined filtrates and the residue was dissolved in 50 ml. of methanol. The methanol solution was neutralized with 10% methanolic potassium hydroxide, and then 5.37 g. (0.096 mole) of potassium hydroxide dissolved in the minimum amount of methanol was added. The mixture was allowed to stand overnight and then the solution was neutralized with acetic acid at 0°. The black solution was then concentrated to ca. 50 ml.; this resulted in the separation of potassium acetate and a black tar from the solution. The mixture of tar and potassium acetate was poured through a Soxhlet cup, ethyl acetate (ca. 200 ml.) was then added to the filtrate and this solution was used for continuous extraction of the residue in the Soxhlet cup. After two days extraction, the solvent was evaporated; the residue was a viscous tar. This tar was dissolved in the minimum amount of water and was extracted continuously with methylene chloride for two days. The extract was dried and the solvent was evaporated. The residue was a black tar which was not investigated further.

Investigations of dl-5-Deoxyribitol and dl-5-Deoxylyxitol. A mixture of 14.4 g. (0.109 mole) of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran and 60 ml. (0.11 mole) of a 6.32% solution of hydrogen peoxide in t-butyl alcohol, prepared as previously described (50), was

placed in a 250-ml. flask and 6 mg. of osmium tetroxide was added. The mixture was allowed to stand 48 hr. at room temperature and then the solvent was evaporated. Three milliliters of 0.01 N sulfuric acid was added, and the mixture was heated on the steam bath for 1 hr. The acid was neutralized with saturated sodium bicarbonate solution, and 50 ml. of water was then added. This was followed by the dropwise addition of a solution of 3.00 g. (0.079 mole) of sodium borohydride in 50 ml. of water. After the solution had stood overnight, the pH was adjusted to 5.0 with 6 N hydrochloric acid, and the solvent was evaporated. The solid material was then placed in a Soxhlet extractor and was extracted continuously for 15 hr. with absolute ethanol. The ethanol was evaporated from the extract; this yielded 12.0 g. (81%) of a brown sirup that resisted crystallization. The n.m.r. spectrum (25%, D_2O) showed absorptions at 4.79-5.30 (6 squares, complex), 5.80-6.73 (10 squares, complex), and 7.48-9.1 τ (18 squares, complex).

A mixture of 10.0 g. (0.074 mole) of the above sirup, 4.0 g. of Dowex 50W-X8 ion-exchange resin, and 50 ml. of dimethylformamide was boiled under reflux for 1 hr. The mixture was filtered and the solvent was removed by distillation *in vacuo*. To the resulting sirup contained in a 50-ml. round-bottomed flask was added 3.0 g. of Dowex 50W-X8 ion-exchange resin. The flask was fitted with an apparatus for vacuum distillation and the reaction vessel was slowly heated to 160-170°. The heating was continued until no more material distilled, This yielded 4.60 g. (53%) of a sirup, that showed b.p. 110-125°/1.0-2.5 mm. Redistillation of the resulting sirup *in vacuo* , using a micro spinning-band column, yielded 3.84 g. of a sirup that showed b.p. 80-83°/0.8 mm. The

n.m.r. spectrul of this preparation showed absorptions at 3.90-4.38 (complex), 5.21 (HOD), 5.58-5.79 (complex), 6.10-6.54 (complex), 8.10-8.52 (complex), 8.75 (doublet, J = 6), and 8.81 τ (doublet, J = 6).

To a solution of 1.415 g. (10.4 mmole) of dl-5-deoxyribitol and dl-5-deoxylyxitol in 50 ml. of dry pyridine was added dropwise 5.83 g. (41.6 mmole) of benzoyl chloride. When the addition was complete, the mixture was allowed to stand overnight; 12.0 g. (0.143 mole) of sodium bicarbonate dissolved in the minimum amount of water was then added. After standing 2 hr., the mixture was extracted with three 75-ml. portions of chloroform. The combined chloroform extracts were extracted with two 150-ml. portions of 2 N hydrochloric acid. The chloroform extract was then dried and the solvent was removed; this yielded 2.39 g. (41.6%) of a sirup that resisted crystallization. This sirup was chromatographed over 50.0 g. of silicic acid using chloroform (fraction volume, 25 ml.). Fractions 11-19 were combined and yielded 184 mg. of crystalline material, m.p. 60-70°. After one recrystallization from methanol-water and two recrystallizations from methanol, the analytical sample showed m.p. 80.5-82°.

Anal.	$C_{33}H_{28}O_8$	Calc'd: C, 71.73; H, 5.11
	(552.6)	Found : C, 72.77; H, 5.98

4-Oxo-cis-2-pentenal

Twenty grams (0.139 mole) of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran was dissolved in 100 ml. of distilled water and the solution was allowed to stand for 16 hr. at room temperature. The mixture was then extracted continuously with ether for 12 hr. The ether extract was dried and the solvent was evaporated. Distillation of the residue

in vacuo yielded a fraction (1.58 g.), b.p. 50-64°/15 mm. that consisted of starting material (shown by n.m.r.) and a little 4-oxo-*cis*-2-pentenal, and a second fraction (6.40 g., 46.6%), b.p. 64-72°/15 mm., of 4-oxo-*cis*-2-pentenal [lit. (34), b.p. 67-68°/11 mm.]. Most of the fraction of b.p. 64-72°/15 mm. distilled at 70°/15 mm.

The n.m.r. spectrum (neat) of the compound showed adsorptions at 0.08 (1H, doublet, J = 6.8), 2.86 (1H, doublet, J = 11.8), 3.84 (1H, doublet, J = 11.8, each component split into a doublet, J = 6.8), and 7.62 τ (3H, singlet). The infrared spectrum (film) of the compound showed λ_{max} 3.31, 5.90, 7.30, 8.60, 10.99, 11.38, and 13.39 μ, among others.

cis-2-Pentene-1,4-diol

Forty-eight and nine-tenths grams of *cis*- and *trans*-2,5-dimethoxy-2,5-dihydro-2-methylfuran (0.333 mole) and 258 ml. of distilled water (14.31 mole) were mixed in a 500-ml. Erlenmeyer flask and swirled occasionally until solution had taken place (*ca.* 1 hr.). After standing 16 hr. at room temperature, the mixture was heated at 50° for 2 hr. The cloudy, orange solution was added dropwise to a solution, which had been cooled to 0° in an ice-acetone bath, of 8.00 g. (0.206 mole) of sodium borohydride in the minimum amount of distilled water. The rate of addition was controlled so that a temperature of 0° was maintained. When the addition was complete the solution was removed from the ice-acetone bath and was allowed to stand at room temperature for 20 hr. The solution was then concentrated to *ca.* 180 ml. and was extracted continuously for three days with methylene chloride. The methylene chloride extract was dried and the solvent was evaporated. The residue was then distilled *in vacuo*; this yielded 23.82 g. of a mixture that showed b.p.

83-87°/1.0 mm., $\eta_D^{24^\circ}$ 1.4656, and consisted of 84.1% of cis-2-pentene-1,4-diol and 15.9% of 1,4-pentanediol (59% yield of cis-2-pentene-1,4-diol, 10.5% yield of 1,4-pentanediol). The n.m.r. spectrum (50%, deuteriochloroform) of the preparation showed absorptions at 4.25-4.50 (9 squares, complex), 5.70-5.92 (16 squares, complex), 6.00-6.67 (4 squares, complex), 8.08-8.64 (3.5 squares, complex), and 8.66-8.91 τ (17.2 squares, two doublets, J = 6.0 and J = 6.5). The infrared spectrum (film) showed λ_{max} 2.98, 3.35, 7.33, 7.73, 9.49, 9.87, and 10.95 μ, among others.

The composition of the above mixture was determined by quantitative catalytic hydrogenation. To 1.25 g. of five per cent platinium on carbon in 25 ml. of 95% ethanol that had been equilibrated with hydrogen at 11.5° and 739.1 mm. was added 1.2610 g. of the above mixture dissolved in 10 ml. of 95% ethanol. After stirring for 64 min. the uptake of hydrogen ceased at 231 ml. (10.3 mmole). It was therefore concluded that the mixture contained 10.3 mmole (1.061 g., 84.1%) of cis-2-pentene-1,4-diol and 200 mg. of 1,4-pentanediol (15.9%).

Attempted Cyclization of cis-2-Pentene-1,4-diol

A mixture of 7.20 g. of cis-2-pentene-1,4-diol (containing 16.5% of 1,4-pentanediol, and, therefore, 6.07 g. of cis-2-pentene-1,4-diol, 59.5 mmole) and 2.20 g. of Dowex 50W-X8 ion-exchange resin was placed in a 25-ml. round-bottomed flask that had been fitted with a distillation apparatus. The reaction vessel was placed in a sand bath and the mixture was slowly heated to 130°; at this temperature distillation began. The temperature of the sand bath was maintained between 130-140° and when no more material distilled, the distillate was extracted with three 20-ml. portions of ether. The combined ether extracts were dried and the

solvent was evaporated. Distillation of the residue, using a micro spinning band column, yielded a fraction (450 mg.) of 2-methyltetrahydrofuran, b.p. 73-75° (46%, based on the 1,4-pentane-diol in the starting material) [lit. (38), b.p. 78-79°]. The n.m.r. spectrum of 2-methyltetrahydrofuran showed adsorptions at 5.88-6.41 (3H, complex), 7.82-8.55 (4H, complex), and 8.79 τ (3H, doublet, J = 6). A second fraction of trans-2-pentenal followed the 2-methyltetrahydrofuran; this fraction (4.02 g., 80.5%) had b.p. 110-115° [lit. (36), b.p. 121.5-123°]. The n.m.r. spectrum of trans-2-pentenal showed adsorptions at 0.47 (1H, doublet, J = 7.5), 3.05 (1H, doublet, J = 16; each component split into a triplet, J = 6), 3.91 (1H, doublet, J = 16; each component split into a doublet, J = 7.5; each component split into a triplet, J = 1.5), 7.68 (2H, a quartet, J = 7.5; each component split into a doublet, J = 6; each component split into a triplet, J = 1.5), and 8.88 τ (3H, triplet, J = 7.5).

A 2,4-dinitrophenylhydrazone of the trans-2-pentenal was prepared by the usual method (40) and showed m.p. 158-160° [lit. (39), m.p. 159-159.5°].

dl-5-Deoxyribitol and dl-5-Deoxylyxitol

A solution of 50.6 g. of a mixture of 84.9% cis-2-pentene-1,4-diol (42.9 g., 0.42 mole) and 15.1% of 1,4-pentanediol (7.7 g., 0.076 mole) in 50 ml. of water was placed in a 250-ml. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, a thermometer, and an addition funnel. The solution was placed in an ice bath and 0.1 g. of osmium tetroxide dissolved in 5 ml. of water was added while stirring. The solution immediately turned black and to it was added dropwise, while stirring, 59.0 g. (0.52 mole) of 30% hydrogen

peroxide solution. The rate of addition was regulated so as to maintain a temperature of 45-50°. When the addition was complete (ca. 1 hr.), 0.5 g. of zinc dust was added and the solution was filtered. The solvent was evaporated, and 46.0 g. of a viscous brown sirup was obtained that resisted crystallization. Assuming all the 1,4-pentanediol (7.7 g.) in the starting material was carried through to the product 38.3 g. (66%) of a mixture of dl-5-deoxyribitol and dl-5-deoxylyxitol was obtained.

The infrared spectrum (film) of the preparation showed λ_{max} 2.95, 3.41, 5.81 (weak), 6.23, 6.89, 7.12, and 7.29 μ, among others.

Benzoate Derivative. A solution of 3.5 g. of a mixture of dl-5-deoxyribitol, dl-deoxylyxitol, and 1,4-pentanediol in 35 ml. of dry pyridine was cooled in an ice bath and 17.0 g. (121.5 mmole) of benzoyl chloride was added dropwise while stirring and cooling. Assuming that 46.0 g. of the starting material contained 7.70 g. of 1,4-pentanediol, 3.5 g. of the starting material would contain 2.91 g. (21.4 mmole) of dl-5-deoxyribitol and dl-5-deoxylyxitol and 0.59 g. (5.77 mmole) of 1,4-pentanediol. When the addition was complete, the mixture was allowed to stand overnight and was then poured into 500 ml. of water. Solid sodium bicarbonate was added until no more carbon dioxide was evolved. After standing 1 hr. the mixture was extracted with three 100-ml. portions of methylene chloride. The combined extracts were dried and the solvent was evaporated; this yielded 13.1 g. (96.5% yield of a mixture of benzoates of dl-5-deoxyribitol, dl-5-deoxylyxitol, and 1,4-pentanediol) of a brown viscous sirup. Crystallization of the above sirup from 50 ml. of methanol gave a brown crystalline solid, which after recrystallization from methanol-ethyl acetate (1:5), gave 4.70 g. (39.8%) of a crystalline mixture of dl-5-deoxy-

ribitol and dl-5-deoxylyxitol tetrabenzoates that showed m.p. 124-131°. The two components were present in a ratio of approximately 5:4 as shown by the n.m.r. spectrum. The filtrate from the first crystallization contained 6.78 g. of a brown sirup that was not investigated further. A small portion (ca. 1 g.) of the crystallized material was chromatographed over silicic acid (ca. 20 g.) using chloroform and was then recrystallized twice from methanol-ethyl acetate (1:5) for elemental analysis. The analytical sample showed m.p. 132-136°.

Anal. $C_{33}H_{28}O_8$ (552.6) Calc'd: C, 71.72; H, 5.40
Found : C, 71.86; H, 5.19

The n.m.r. spectrum of the mixture (15%, deuteriochloroform) showed adsorptions at 1.75-2.25 (8H, complex), 2.3-2.9 (12H, complex), 3.84-4.50 (3H, complex), 4.84-5.58 (2H, complex), and 8.30-8.58 τ (3H, two doublets, J = 6 and J = 6). The infrared spectrum showed λ_{max} 3.23, 3.33, 5.80, 6.23, 6.30, 6.90, 10.69, and 11.78 μ, among others.

A portion (1.40 g.) of the crude product from another preparation of the mixture of benzoates was chromatographed over acid-washed aluminia (140 g., column 1.3 cm. x 54.0 cm.) using benzene (fraction volume 50 ml.). Fractions 1-4 contained no material and were discarded; fraction 5 contained 201 mg. of crystalline material and showed only one doublet in the n.m.r. spectrum in the region the original mixture showed two doublets. An analytical sample was prepared by recrystallizing fraction 5 three times from methanol-ethyl acetate (1:5); it showed m.p. 141-141.5°.

Anal. $C_{33}H_{28}O_8$ (552.6) Calc'd: C, 71.72; H, 5.40
Found : C, 71.82; H, 5.13

The n.m.r. spectrum of fraction 5 (15%, deuteriochloroform) showed

adsorptions at 1.81-2.14 (8H, complex), 2.40-2.80 (12H, complex), 3.91-4.61 (3H, complex), 4.88-5.67 (2H, complex), and 8.45 τ (3H, doublet, J = 6). The infrared spectrum showed λ_{max} 3.32, 5.80, 6.25, 6.90, 7.61, 7.91, 9.04, 12.41, and 14.09 μ, among others.

dl-3-Nordihydrodideoxystreptose and dl-3-Nor-4-epidihydrodideoxystreptose

Thirty-five grams of a mixture consisting of dl-5-deoxyribitol and dl-5-deoxylyxitol (29.2 g., 0.214 mole) and 1,4-pentanediol (5.8 g., 0.056 mole) (assuming all the 1,4-pentanediol in the starting material for this mixture was carried through) was placed in a 100-ml. round-bottomed flask that had been fitted with an apparatus for vacuum distillation. Dowex 50W-X8 ion-exchange resin (9.2 g.) was added and slow heating was begun under a vacuum of 0.25 mm. The temperature of the sand bath, in which the reaction vessel was placed, was increased to 150° over a period of 0.5 hr. At this temperature distillation began, and as the rate of distillation decreased the temperature of the sand bath was gradually increased. When distillation ceased, the temperature of the bath was 190-200°. The distillate was redistilled in vacuo and distilled almost completely over the range 79-82°/0.5 mm.; this yielded 20.0 g. of a colorless sirup that consisted of a mixture of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose (16.3 g., 64%) and dl-1,4-pentanediol (3.7 g.; 64% of that presumed to be present in the starting material). The composition of the mixture was determined by the n.m.r. spectrum (40%, deuteriochloroform), which showed adsorptions at 5.50 (OH), 5.80-6.65 (19 squares, complex), 8.10-8.60 (3 squares, complex), and 8.60-9.00 τ (9.5 squares, 2 doublets, J = 6; J = 6). Redistillation of the preparation in vacuo did not accomplish appreciable separation of the mixture into its components

(shown by n.m.r.).

The infrared spectrum of the preparation showed λ_{max} 2.95, 3.39, 6.90, 7.27, 8.10, and 12.07 μ, among others.

Benzoate Derivative. To a solution of 2.51 g. of the above mixture of dl-3-nordihydrodideoxystreptose, dl-3-nor-4-epidihydrodideoxystreptose (2.04 g., 17.3 mmole), and dl-1,4-pentanediol (0.48 g., 4.62 mmole) in 20 ml. of dry pyridine, 12.5 g. (88.5 mmole) of benzoyl chloride was added dropwise, while cooling. When the addition was complete, the mixture was allowed to stand overnight and was then poured into saturated sodium bicarbonate solution (400 ml.). After standing 1 hr., the solution was extracted with four 100-ml. portions of methylene chloride. The combined methylene chloride extract was washed with three 200-ml. portions of 2.5% hydrochloric acid, 100 ml. of saturated sodium bicarbonate solution, and finally with two 100-ml. portions of water. The methylene chloride extract was dried and the solvent was evaporated; this gave 11.00 g. (154.8% based on the composition of the starting material) of a tan viscous sirup. The infrared spectrum of the sirup showed absorptions at 5.62 and 5.82 μ, which indicated that benzoic anhydride was present. The crude product (11.00 g.) was dissolved in 10 ml. of pyridine and was placed in a 250-ml. Erlenmeyer flask that contained 100 ml. of saturated sodium bicarbonate solution. While stirring magnetically overnight, a portion of the solution was lost; the remainder of the solution was extracted with three 75-ml. portions of methylene chloride. The combined methylene chloride extract was extracted with 2.5% hydrochloric acid until the extract no longer smelled of pyridine. The solution was then washed with water (ca. 100 ml.), dried, and the solvent was evaporated.

This yielded 4.61 g. (65% based on the composition of the starting material) of a tan sirup that resisted crystallization. This sirup (4.17 g.) was chromatographed over aluminia (417 g., column dimensions, 0.54 cm. x 130 cm.), using benzene. Fraction 1 (520 ml.) contained no material. Fraction 2 (90 ml.) contained 206 mg. of material. Fraction 2 was shown by n.m.r. to be a mixture of the dibenzoates of dl-3-nordihydrodideoxystreptose, dl-3-nor-4-epidihydrodideoxystreptose, and dl-1,4-pentanediol. The n.m.r. spectrum (20%, deuteriochloroform) showed absorptions at 1.82-2.15 (complex), 2.40-2.84 (complex), 4.10-4.28 (complex), 4.38-4.52 (complex), 4.67-5.08 (complex), 5.50-5.92 (complex), 7.79-8.34 (complex), and 8.34-8.79 τ (three doublets). Fractions 3-21 (fraction volume 40 ml.) contained a total of 1.754 g. of colorless oil that was not investigated further. Fraction 22 (180 ml.) contained 171 mg. of a colorless oil that was shown to be a mixture of the dibenzoates of dl-3-nor-4-epidihydrodideoxystreptose, dl-3-nordihydrodideoxystreptose, and dl-1,4-pentanediol by the n.m.r. spectrum which showed complex absorptions at 1.82-2.23, 2.38-2.94, 3.95-4.96, 5.32-6.18, 7.63-7.72, 7.87-8.10, and 8.21-8.87 τ. Fraction 2 was enriched in the dibenzoate of dl-1,4-pentanediol and fraction 22 was enriched in the dibenzoates of dl-3-nor-4-epidihydrodideoxystreptose and dl-3-nordihydrodideoxystreptose.

3,5-Dinitrobenzoyl Derivatives. A solution of 0.50 g. of the mixture consisting of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose (312 mg., 2.65 mmole) and dl-1,4-pentanediol (188 mg., 1.81 mmole) in 20 ml. of dry pyridine was cooled in an ice bath; to this solution 3.90 g. (16.9 mmole) of freshly recrystallized 3,5-dinitrobenzoyl chloride was added in small portions. After the addition was

complete, the mixture was heated to boiling and then was cooled and poured into 10 ml. of water that contained pieces of ice; to this was added 75 ml. of saturated sodium bicarbonate solution. The solution was allowed to stand 0.5 hr. and was then extracted with three 50-ml. portions of chloroform. The combined chloroform extract was then washed with 1.5% hydrochloric acid until the chloroform no longer smelled of pyridine. The chloroform extract was then washed with saturated sodium bicarbonate solution (ca. 40 ml.) and with water (ca. 50 ml.). The chloroform extract was dried, and the solvent was evaporated; this yielded 2.55 g. (112% based on the composition of the starting mixture) of a yellow glass that resisted crystallization. The mixture was chromatographed over silicic acid (20.0 g.) using chloroform. The fractions eluted before the first pale yellow band contained no material and were discarded. The next fraction, which contained the first pale yellow band, was collected and contained 1.313 g. of a semisolid gum. A fraction (0.293 g.) was then collected and was followed by a second pale yellow band, which contained 1.050 g. of a pale yellow glass. The fraction that weighed 1.313 g. resisted crystallization and was rechromatographed over silicic acid (20.0 g.) using chloroform. The fractions eluted before the yellow band contained no material and were discarded. The yellow band was collected and contained 0.989 g. of semicrystalline material; this was recrystallized from benzene and furnished 509 mg. (57.1% of pale yellow dl-1,4-bis-(3,5-dinitrobenzoyloxy)-pentane, which melted incompletely at 55-65°, resolidified at 80-85°, and melted again at 151-154°. If the resulting melt was allowed to cool and crystallize, the material melted at 152-154°. An analytical sample was prepared by recrystallizing a portion of the material from benzene. The

analytical sample melted at 59-67°, resolidified and melted again at 153-154.5° [lit. (58), m.p. 138°, resolidifying and melting again at 151-152°].

Anal. $C_{19}H_{16}N_4O_{12}$ (492.4) Calc'd: C, 46.34; H, 3.28; N, 11.38
Found : C, 46.19; H, 3.34; N, 11.21

The n.m.r. spectrum (20%, deuteriochloroform) of the compound showed adsorption at 0.64-0.88 (6H, complex), 4.34-5.00 (1H, complex), 5.24-5.66 (2H, complex), 7.66-8.28 (4H, complex), and 8.50 τ (3H, doublet, J = 6). The infrared spectrum (KBr pellet) showed λ_{max} 3.20, 5.81, 6.14, 6.49, 7.46, 7.83, 8.59, 10.90, 13.71, and 13.86 μ, among others.

The second yellow band (1.050 g.) that was eluted from the first column resisted crystallization and was rechromatographed over aluminia (45 g.), using 10% methanol in chloroform. The fractions eluted before the yellow band contained no material and were discarded; the yellow band was collected as one fraction and contained 926 mg. of the bis-3,5-dinitrobenzoyl derivative of dl-3-nordihydrodideoxystreptose and the bis-3,5-dinitrobenzoyl derivative of dl-3-nor-4-epidihydrodideoxystreptose. After crystallization from chloroform-methanol and three recrystallizations from acetone, 350 mg. (26.1% based on the composition of the starting mixture) of material was obtained and showed m.p. 178-181°. A portion of this was recrystallized from acetone three more times for elemental analysis and showed m.p. 183.5-184°.

Anal. $C_{19}H_{14}N_4O_{13}$ (506.3) Calc'd: C, 45.19; H, 2.79; N, 11.07
Found : C, 45.33; H, 2.63; N, 10.79

The infrared spectrum (KBr pellet) showed λ_{max} 3.22, 5.79, 6.51, 6.53, 6.90, 7.50, 10.94, 13.76, and 14.00 μ, among others.

Phthalate Derivatives. A solution of 1.01 g. of the mixture

consisting of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose (360 mg., 5.33 mmole) and dl-1,4-pentanediol (380 mg., 3.65 mmole) in 20 ml. of dry pyridine was prepared; to this was added 4.0 g. (27 mmole) of freshly sublimed phthalic anhydride. The solution was allowed to stand 1.5 hr. at room temperature and was then heated on the steam bath overnight; this was followed by the addition of 50 ml. of saturated sodium bicarbonate solution. The solution was allowed to stand 45 min. and then was extracted with three 75-ml. portions of chloroform. The combined chloroform extracts were dried and the solvent was evaporated; no material was obtained. The pH of the aqueous solution waas adjusted to 1.5 with 2.5% hydrochloric acid and was extracted with three 75-ml. portions of chloroform. The combined chloroform extracts were dried and the solvent was evaporated. This yielded 3.18 g. (87% based on the composition of the starting material) of a tan glass that resisted crystallization. The glass was chromatographed over silicic acid (50 g.), using chloroform. The fractions eluted before the first opaque band contained no material and were discarded. The first opaque band (926 mg.) was collected and was crystallized from benzene. This gave 843 mg. (57.6%) of the bis-hydrogen phthalate of dl-1,4-pentanediol, m.p. 139-141.5°. A portion of this material was recrystallized three times from benzene for elemental analysis and showed m.p. 141.5-143°.

Anal.	$C_{21}H_{20}O_8$	Calc'd: C, 63.00; H, 5.03
	(400.4)	Found : C, 62.54; H, 5.03

The n.m.r. spectrum (20%, deuteriochloroform) of the compound showed absorptions at -2.34 (2H, singlet), 2.04-2.56 (8H, complex), 4.56-5.12 (1H, complex), 5.22-6.14 (2H, complex), 8.00-8.34 (4H, complex), and

8.70 τ (3H, doublet, J = 6). The infrared spectrum (KBr pellet) of the compound showed λ_{max} 3.33, 5.85, 5.97, 7.16, 7.84, 8.96, 12.68, and 13.46 μ, among others.

The material eluted before the second opaque band amounted to 65 mg. and was not investigated further. The second opaque band (1.88 g.) was then eluted and was shown by n.m.r. to be a mixture of the bis-hydrogen phthalate of dl-1,4-pentanediol and the bis-hydrogen phthalates of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose. This mixture resisted crystallization and was rechromatographed over silicic acid (50 g.), using chloroform. Two incompletely separated opaque bands that moved very slowly were visible on the column after ca. 150 ml. of chloroform had been collected. The eluent was then changed to 2.5% methanol in chloroform and the first opaque band (357 mg.), which clearly separated from the trailing band, was collected. This material was shown by n.m.r. to be the bis-hydrogen phthalate of dl-1,4-pentanediol. This band was followed by 41 mg. of material that was not investigated further, and then a second opaque band (712 mg.) was collected. This material crystallized from benzene-methanol (5:1) after standing at 0° for three months and showed m.p. 170-174°. The solid material was collected and recrystallized from water-methanol. This furnished 300 mg. (13.6%) of a mixture of bis-hydrogen phthalates of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose, m.p. 179.5-183.5°. A portion of this material was recrystallized three times from benzene-methanol (5:1) for elemental analysis and showed m.p. 178.5-181.5°.

Anal. $C_{21}H_{18}O_9$ (414.4) Calc'd: C, 60.86, H, 4.38
Found : C, 61.40; H, 4.77

The n.m.r. spectrum (saturated, deuteriochloroform) of the preparation showed adsorption at 0.10 (2H, singlet), 1.94-2.66 (8H, complex), 4.00-4.20 (1H, complex), 4.66-4.98 (1H, complex), 5.34-6.40 (3H, complex), and 8.62 τ (3H, doublet, J = 6). The infrared spectrum of the preparation showed λ_{max} 3.29, 3.70, 3.88, 5.80, 5.94, 6.30, 6.39, 7.80, 9.37, 11.71, and 13.47 μ, among others.

dl-2,3,5-Trideoxy-2,3-dibromoarabitol and dl-2,3,5-Trideoxy-2,3-dibromoxylitol

A solution of 67.0 g. of a mixture of 1,4-pentanediol (10.65 g., 0.103 mole) and cis-2-pentene-1,4-diol (56.35 g., 0.553 mole) in 130 ml. of methylene chloride was placed in a 500-ml. three-necked flask that had been fitted with a mechanical stirrer, a condenser, and an addition funnel. The mixture was cooled in an ice bath, and a solution of bromine in methylene chloride (1:4) was added dropwise until the color of bromine persisted. This color was then discharged with a few drops of the starting diol mixture. As the solvent was evaporated at 35° from the pale pink solution, crystalline material separated, and the mixture acquired a dark purple color. A portion (ca. 2 g.) of the suspension of crystalline material in the dark purple sirup was removed and was mixed with ca. 10 ml. of chloroform. The mixture was filtered, and the solid material was washed with chloroform. After the material was dried, it showed m.p. 124-126°. The solvent was evaporated from the filtrate; the resulting dark purple sirup resisted crystallization. A portion of the crystalline material was recrystallized three times from benzene-methanol (4:1) for elemental analysis and showed m.p. 125.5-126°.

Anal. $C_5H_{10}O_2Br_2$ (261.9) Calc'd: C, 22.78; H, 3.85; Br, 61.01
Found : C, 23.09; H, 3.89; Br, 61.24

The n.m.r. spectrum (saturated, pyridine) of the compound showed absorptions at 3.43 (2H, singlet), 4.97 (1H, two doublets, J = 7, J = 7), 5.40-6.08 (4H, complex, and 8.48 τ (3H, doublet, J = 5). The infrared spectrum of the compound showed λ_{max} 2.99, 5.75 (weak), 6.95, 7.36, 7.97, 8.20, 8.89, 9.63, 9.90, 10.48, and 13.56 μ, among others.

2-Methyl-3,4-trans-dibromotetrahydrofurans

The entire amount of purple sirup from the above preparation was mixed with 10 g. of p-toluenesulfonic acid monohydrate in a 250-ml. round-bottomed flask that had been fitted with an apparatus for vacuum distillation. The reaction vessel was heated in an oil bath to 150-160°; at this temperature, distillation began under water aspirator vacuum. The distillate consisted of two phases. The temperature of the oil bath was then raised to 160-165° to maintain distillation of the product at the rate of one drop every two seconds. When the rate of distillation began to decrease, the temperature of the oil bath was slowly increased to 180°. When no more material distilled, methylene chloride (ca. 100 ml.) was added to the distillate. The water layer was discarded. The methylene chloride solution was washed with two 30-ml. portions of saturated sodium bicarbonate solution, dried, and the solvent was evaporated. The residue was distilled in vacuo and yielded 86.45 g. (63.5%, based on the amount of cis-2-pentene-1,4-diol in the starting diol mixture) of 2-methyl-3,4-trans-dibromotetrahydrofurans that showed b.p. 84-89°/15 mm. A portion of material obtained in a similar preparation (b.p. 88-92°/15 mm.) was redistilled on a lab-size spinning band-column for elemental analysis.

The analytical sample showed b.p. 91°/15 mm.

Anal. $C_5H_8OBr_2$ (243.9) Calc'd: C, 24.61; H, 3.35; Br, 65.51
Found : C, 24.52; H, 3.17; Br, 65.51

The n.m.r. spectrum (neat) of the compound showed absorptions at 5.13-6.13 (5H, complex), 8.60 (3H, doublet, J = 6), and 8.69 τ (3H, doublet, J = 6). The infrared spectrum (film) of the compound showed λ_{max} 3.30, 3.44, 7.27, 7.67, 7.90, 8.60, 9.14, 9.60, 11.40, and 12.03 μ, among others.

2-Methyl-2,5-dihydrofuran

A mixture of 150 ml. of freshly distilled n-hexyl alcohol and zinc dust (94 g., 1.44 atom) was placed in a 500-ml. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an addition funnel, and an apparatus for distillation. The reaction vessel was heated to 140°. A solution of 160 g. (0.651 mole) of the 2-methyl-3,4-trans-dibromotetrahydrofurans in 150 ml. of freshly distilled n-hexyl alcohol was added at a rate that maintained moderate distillation. When the addition was complete, the reaction mixture was distilled until the temperature of the distillate reached 155°. The distillate was redistilled, using a lab-size spinning band column, and the fraction that showed b.p. 70-78° (35.9 g., 65%) was collected as crude 2-methyl-2,5-dihydrofuran. This material was combined with 20.8 g. of crude 2-methyl-2,5-dihydrofuran from another preparation and was distilled from calcium hydride using a lab-size spinning band column. This gave 49.86 g. (58.6% yield based on the amount of the 2-methyl-3,4-trans-dibromotetrahydrofurans used in both preparations) of 2-methyl-2,5-dihydrofuran that showed b.p. 74-76°, $\eta_D^{24°}$ 1.4213 [lit. (41), b.p. 74-76°, $\eta_D^{25°}$ 1.4195].

The n.m.r. spectrum (neat) of the compound showed absorptions at 4.00-4.36 (2H, complex), 4.92-5.37 (3H, complex), 5.39-5.58 (2H, complex), and 8.84 τ (3H, doublet, J = 6). The infrared spectrum (film) of the compound showed λ_{max} 3.36, 3.50, 6.08, 6.24, 6.93, 7.45, 9.26, 10.12, 12.12, and 13.64 μ, among others.

Hydroxylation of 2-Methyl-2,5-dihydrofuran Using the Silver Acetate-Iodine-Wet Acetic Acid Reagent

In a 2-l. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, a reflux condenser, and a powder funnel was placed 1.141 l. of glacial acetic acid, 93.86 g. (0.557 mole) of silver acetate, and 21.00 g. (0.25 mole) of 2-methyl-2,5-dihydrofuran. Finely powdered iodine (66.62 g., 0.264 mole) was added over a period of 0.5 hr., while stirring. The mixture was stirred for an additional 0.5 hr., and then 4.501 g. (0.25 mole) of water in 100 ml. of glacial acetic was added. The mixture was then heated at 85-90°, while stirring, for 3 hr. After cooling, solid sodium chloride (ca. 20 g.) was added and the mixture was stirred for 10 min. The mixture was filtered, and the insoluble material was washed thoroughly with hot chloroform. The solvent was evaporated, and the residue was mixed with 200 ml. of chloroform; the mixture was filtered, and the solvent was evaporated. The pH of the residue was adjusted to 7.0 with ca. 10% methanolic potassium hydroxide, and 19.6 g. of potassium hydroxide dissolved in the minimum amount of methanol was added. After standing overnight at room temperature, the black mixture was concentrated to a sirup and water (ca. 100 ml.) was added. The solution was extracted continuously for 48 hr. with methylene chloride, and the solvent was evaporated from the extract. Distillation of the resulting

black sirup, in vacuo, yielded 23.55 g. (79.7%) of material that showed b.p. 82°/0.6 mm. A portion of the preparation was redistilled twice for elemental analysis and showed b.p. 82°/0.6 mm., $\eta_D^{25°}$ 1.4655. GLC analysis (30% SE-30; Helium inlet pressure, 50 psig; C.T. 144°) using an Autoprep instrument (Wilkens Instrument Co.) failed to separate the two diols and showed one peak at R.T. 19.8 min.

Anal.	$C_5H_{10}O_3$	Calc'd: C, 50.84; H, 8.53
	(118.1)	Found : C, 50.92; H, 8.38

The n.m.r. spectrum (45%, deuterium oxide) showed absorptions at 2.31 (HOD), 5.62-6.46 (5H, complex), and 8.76 τ (3H, doublet, J = 6). The infrared spectrum (film) of the preparation showed λ_{max} 2.90, 3.33, 6.90, 7.25, 8.25, 9.26, 9.75, 10.16, 11.64, and 12.10 μ, among others.

Phthalate Derivative. To a solution of 1.00 g. (0.0085 mole) of the above preparation in 15 ml. of dry pyridine was added 3.151 g. (0.0213 mole) of freshly sublimed phthalic anhydride. After the phthalic anhydride had dissolved, the mixture was heated on the steam bath overnight, was cooled, and was poured into a saturated sodium bicarbonate solution (ca. 50 ml.). After standing 1 hr., the mixture was extracted with three 50-ml. portions of chloroform. This chloroform extract was discarded; the mixture was made acidic (pH 1) with 2% hydrochloric acid, and was then extracted with three 50-ml. portions of chloroform. The combined chloroform extract was dried, and the solvent was evaporated. This yielded 3.14 g. (89.1%) of a brown glass that was dissolved in ca. 10 ml. of benzene. This solution was seeded with material previously obtained crystalline (42), and after two days at 5°, crystallization was complete. The mixture was filtered, and 2.675 g. (72%) of white crystalline material,

which showed m.p. 178.5-180°, was obtained. A portion of this material was recrystallized twice from benzene-methanol (5:1) for elemental analysis and showed m.p. 181.5-183.4°.

Anal.	$C_{21}H_{18}O_9$	Calc'd: C, 60.87; H, 4.38
	(414.4)	Found : C, 61.26; H, 4.48

The n.m.r. spectrum (20%, acetone-d_6) showed absorptions at 2.00-2.61 (8H, complex), 2.77 (2H, broad singlet), 4.29 (1H, doublet, J = 5.6; each component of which split into a doublet, J = 5.5; each component of which split into a doublet, J = 3.9), 4.88 (1H, doublet, J = 5.6; each component of which split into a doublet, J = 7.4), 5.61 (1H, doublet, J = -10.2; each component of which split into a doublet, J = 5.5), 5.89 (1H, quartet, J = 6.3; each component of which split into a doublet, J = 7.4), 6.02 (1H, doublet, J = -10.2; each component of which split into a doublet, J = 3.9), and 8.63 τ (3H, doublet, J = 6.3). The infrared spectrum showed λ_{max} 3.38, 5.80, 7.11, 7.81, 8.88, 9.34, 9.69, 11.39, 11.71, 12.74, and 13.50 μ, among others.

Partial resolution using brucine. The bis-hydrogen phthalate (5.00 g., 12.05 mmole) from above was dissolved in the minimum amount of hot acetone and to this solution was added a solution of brucine (4.75 g., 12.05 mmole) in the minimum amount of hot acetone. The solution failed to produce crystalline material upon cooling and after the solvent was evaporated the resulting sirup resisted crystallization from a variety of solvents. The sirup was dissolved in 25 ml. of acetone and 4.75 g. (12.05 mmole) of brucine dissolved in the minimum amount of acetone was added. This solution failed to produce crystalline material upon cooling or slow concentration to a sirup. The sirup was then dissolved

in the minimum amount of hot benzene-isopropyl ether (ca. 1:2) and cooled slowly. A gum separated from the solution and after standing two days at 0° 4.594 g. of crystalline material that showed m.p. 136-5-140° separated from the solution. The crystalline material (400 mg.) was dissolved in 10 ml. of absolute ethanol and the pH of the solution was adjusted to 1.0 with 10% hydrochloric acid. The solution was then extracted with three 15-ml. portions of chloroform. The combined chloroform extract was washed with four 20-ml. portions of water, one 20-ml. portion of 10% hydrochloric acid, and finally with two 20-ml. portions of water. The chloroform solution was dried and the solvent was evaporated; this yielded 237.5 mg. of a brown sirup. This sirup was dissolved in ca. 50 ml. of chloroform; the chloroform solution was washed with four 20-ml. portions of 10% hydrochloric acid and with two 20-ml. portions of water. After the solvent was dried and evaporated, the chloroform extract yielded 147.3 mg. of a brown glass that resisted crystallization and showed $[\alpha]_D$ +6.32° ± 1.3° (c 2.325, 95% ethanol).

The remainder of the brucine salt (4.194 g.) from above was recrystallized from ethanol-acetone (3:1) and 2.372 g. of crystalline material that showed m.p. 137-141° was obtained. A portion (400 mg.) of this material was converted to the noncrystalline bis-hydrogen phthalate (192 mg.) as previously described; the bis-hydrogen phthalate showed $[\alpha]_D$ 19.92° ± 0.83° (c 3.12, 95% ethanol).

The salt (2.372 g.) from the second recrystallization was recrystallized from ethanol-acetone (3:1) and furnished 1.732 g. of material m.p. 139-143°. This material (400 mg.) was converted to the noncrystalline bis-hydrogen phthalate, as described above, which showed $[\alpha]_D$

$44.0^{0} \pm 0.6$ (c 2.54, 95% ethanol).

Hydroxylation of 2-Methyl-2,5-dihydrofuran Using Potassium Permanganate

A mixture of 2-methyl-2,5-dihydrofuran (17.01 g., 0.23 mole) and distilled water (243 ml.) was placed in a 1-l. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an alcohol thermometer, and an addition funnel. The mixture was cooled to -1^{0} in an ice-acetone bath, and a solution of 32.1 g. (0.21 mole) of potassium permanganate in 610 ml. of water was added at a rate so as to maintain a temperature of $2^{0} \pm 1^{0}$. When the addition was complete, the mixture was removed from the ice-acetone bath and was allowed to stand 2 hr. The mixture was then heated on a steam bath 1 hr., filtered, and the insoluble material was washed thoroughly with two 200-ml. portions of boiling water; the filtrate was then concentrated to ca. 125 ml. The aqueous solution was extracted continuously with chloroform until no more material was extracted after 24 hr. extraction (ca. 2.5 days). The combined chloroform extracts were distilled in vacuo and yielded 12.416 g. (52%) of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose that showed b.p. $77^{0}/0.3$ mm. GLC (SE-30, A.I.P. 20 psig, C.T. 66^{0}) analysis of the distilled material showed only one peak at R.T. 9.7 min. A portion of material from another preparation was redistilled for elemental analysis and showed b.p. $77^{0}/0.3$ mm., $\eta_{D}^{24^{0}}$ 1.4692.

Anal. $C_5H_{10}O_3$ (118.1) Calc'd: C, 50.84; H, 8.53
Found : C, 50.57; H, 8.46

The n.m.r. spectrum (20%, chloroform) showed absorptions at 5.43-6.54 (7H, complex) and 8.73 τ (3H, doublet, J = 6). The infrared spectrum showed λ_{max} 2.96, 3.31, 6.93, 7.28, 7.56, 8.27, 9.27, 9.75, 11.60, and

12.09 μ, among others.

bis-p-Nitrobenzoyl Derivative. To a solution of 472 mg. (4.0 mmole) of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose in 20 ml. of dry pyridine was added, in small portions while swirling, 1.484 g. (8.0 mmole) of freshly recrystallized p-nitrobenzoyl chloride. When the addition was complete, the solution was allowed to stand overnight and was then heated on a steam bath for 2 hr. The solution was then cooled, dissolved in 300 ml. of chloroform, and washed with 5% hydrochloric acid until the odor of pyridine had disappeared from the chloroform solution. The chloroform extract was then washed with one 100-ml. portion of 5% sodium bicarbonate and one 100-ml. portion of water. The chloroform extract was dried, and the solvent was evaporated. This yielded 1.588 g. (95.8%) of a yellow glass. Methanol (10 ml.) was added, and the mixture was heated to boiling. Sufficient benzene was then added to the boiling mixture to completely dissolve the reaction product. Slow cooling of the reaction mixture furnished 973 mg. of pale yellow crystalline material that showed m.p. 95-104°. A portion of this material was recrystallized three times from benzene-methanol for elemental analysis. The analytical sample showed m.p. 96.5-119.5°.

Anal.	$C_{19}H_{16}N_2O_9$	Calc'd:	C, 54.81; H, 3.87; N, 6.73
	(416.3)	Found :	C, 55.41; H, 3.93; N, 7.13

The n.m.r. spectrum (20%, deuteriochloroform) of material that had been recrystallized two times showed absorptions at 1.60-2.10 (48 squares, complex), 4.05-4.40 (8.5 squares, four major lines), 4.58-4.50 (4 squares, four major lines), 5.30-6.10 (18 squares, complex), 8.54 and 8.59 τ (17 squares, two doublets, J = 6.0 and J = 6.0).

The infrared spectrum (5%, chloroform) showed λ_{max} 5.75, 6.22, 6.54, 7.42, 7.81, 8.88, 9.06, 9.85, 11.44, and 12.91 μ, among others.

Phthalate Derivative. To a solution of 1.01 g. (8.56 mmole) of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose in 15 ml. of pyridine, 3.803 g. (25.7 mmole) of phthalic anhydride was added. After the phthalic anhydride had dissolved, the solution was heated on a steam bath overnight. The solution was cooled, and 60 ml. of water was added. Solid sodium bicarbonate was then added until the solution was saturated, and after standing 1 hr., the solution was extracted with chloroform until the odor of pyridine had disappeared. The chloroform extract was discarded. The aqueous solution was acidified with 2 N hydrochloric acid to pH 1 and was then extracted with three 100-ml. portions of chloroform. The combined chloroform extract was washed with two 50-ml. portions of water and was dried. Evaporation of the chloroform from the extract furnished 4.21 g. (117%) of a tan glass that resisted crystallization. This material was chromatographed over silicic acid (80 g.) using chloroform. Fraction 1 (750 ml.) contained 203 mg. of brown oil that was discarded. Fraction 2 (1000 ml.) contained 497 mg. of crystalline material. The eluting solvent was then changed to 3% methanol in chloroform. Fraction 3 (200 ml.) contained 2.213 g. of crystalline material. Fraction 4 (200 ml.) contained 1.002 g. of crystalline material. Fraction 5 (300 ml.) contained 65 mg. of material that was discarded. Fractions 2-4 were combined and recrystallized two times from benzene-methanol. The resulting material showed m.p. 178-182°.

The n.m.r. spectrum (20%, acetone-d_6) of the preparation showed absorptions at 2.00-2.68 (14 squares, complex), 3.19 (4 squares, broad

singlet), 4.16-4.50 (2.2 squares, complex), 4.75-5.08 (1 square, three major lines), 5.46-6.41 (5 squares, complex), and 8.65 and 8.75 τ (5.2 squares, two doublets, J = 6 and J = 6).

The infrared spectrum (pellet) showed λ_{max} 3.32, 5.81, 5.92, 6.28, 7.78, 9.36, 11.71, 12.69, and 13.46 μ, among others.

bis-3,5-Dinitrobenzoyl Derivative. dl-3-Nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose (236 mg., 2.0 mmole) was dissolved in 25 ml. of dry benzene that contained 480 mg. (6.07 mmole) of dry pyridine. The solution was cooled in an ice bath and, while swirling, 922 mg. (4.0 mmole) of 3,5-dinitrobenzoyl chloride was added in small portions. When the addition was complete, the solution was allowed to stand overnight and then 10 ml. of water and 20 ml. of benzene were added. The water layer was separated and the benzene solution was washed with 2% hydrochloric acid until the odor of pyridine had disappeared. The benzene solution was washed with two 25-ml. portions of water, dried, and the solvent was evaporated. This yielded 854 mg. (84.2%) of yellow gum that contained crystalline material. The entire amount of crude product was dissolved in the minimum amount of boiling 2-butanone, and the solution was allowed to cool in an ice bath. This furnished 452 mg. (44.5%) of pale yellow crystals that showed m.p. 175.5-179.5°. This material was recrystallized two times from the minimum amount of hot 2-butanone and showed m.p. 180-182°.

The n.m.r. spectrum (saturated, dimethyl sulfoxide-d_6) showed absorptions at 0.64-1.18 (6H, complex), 4.03-4.39 (1H, four broad lines, 4.63 (1H, doublet, J = 6; each component split into a doublet, J = 6), 5.26-6.18 (3H, complex), and 8.62 τ (3H, doublet, J = 6.2).

The infrared spectrum (pellet) of this material was identical with that of a sample obtained (43) previously.

The melting point of a mixture of the material obtained in this preparation and the material obtained previously showed no depression. The melting point observed for the mixture was 180-182.5°.

bis-l-Menthoxyacetate Derivatives. A solution of 1.18 g. (0.01 mole) of the above mixture of dl-3-nordihydrodideoxystreptose and dl-3-nor-4-epidihydrodideoxystreptose in 20 ml. of dry pyridine was cooled to 0° in an ice bath. l-Menthoxyacetyl chloride, prepared as described elsewhere (44) from 4.29 g. (0.02 mole) of l-menthoxyacetic acid, was added dropwise. When the addition was complete, the solution was stirred overnight, poured into water (ca. 200 ml.), and extracted with chloroform. The chloroform extract was washed with 4% hydrochloric acid, dried, and the solvent was evaporated. This yielded 4.773 g. (93.4%) of a brown sirup that resisted crystallization. The infrared spectrum showed λ_{max} 3.35, 5.66, 6.90, 7.28, 7.37, 8.91, 10.21, 11.02, and 11.89 μ, among others.

Synthesis of dl-Dihydrodideoxystreptose And Related Compounds

Synthesis of 2,3-Dimethylfuran

Ethyl 2-Methylfuran-3-carboxylate. To a solution of ethyl acetoacetate (354 g., 3.10 mole) in 680 ml. of pyridine, which was stirred magnetically and cooled in an ice bath, 500 g. (2.55 moles) of a 40% solution of chloroacetaldehyde in water was added dropwise. When the addition was complete, the solution was removed from the ice bath and

was allowed to stand at room temperature overnight. Ether (ca. 500 ml.) was added and the organic layer was separated. The aqueous layer was extracted with two 200-ml. portions of ether and the combined ether extract was washed with 5% hydrochloric acid until the odor of pyridine had disappeared. The ether extract was then shaken with three 100-ml. portions of saturated sodium bisulfite solution and then with two 100-ml. portions of water. The resulting extract was dried, and the solvent was evaporated. Distillation of the residue in vacuo furnished 264.0 g. (67.5%) of ethyl 2-methylfuran-3-carboxylate, b.p. 93°/30 mm. [lit. (45), b.p. 81-84°/18 mm.].

The n.m.r. spectrum (neat) of the compound showed absorptions at 2.62 (1H, doublet, J = 2.1, each component of which was split into a quartet, J = 0.4), 3.28 (1H, doublet, J = 2.1, each component of which was split into a quartet, J = 0.4), 5.68 (2H, quartet, J = 7), 7.43 (3H, quartet, J = 0.4), and 8.69 τ (3H, triplet, J = 7). The infrared spectrum (film) showed λ_{max} 3.28, 5.82, 6.21, 6.56, 7.69, 8.43, 9.13, 10.56, 11.15, 12.77, and 13.57 μ, among others. The above procedure is a modification of that of Winberg et al. (45) who obtained a lower yield (63%) of a product that was contaminated with ethyl acetoacetate.

Ethyl 2-methylfuran-3-carboxylate was also prepared by the method of Gilman et al. (61) and showed b.p. 85-88°/28 mm. (41.5% yield) [lit. (45), b.p. 81-84°/18 mm.].

2-Methyl-3-hydroxymethylfuran. This compound was prepared essentially as described in the literature (45). However, it was found that when the molar ratio of lithium aluminum hydride to ethyl 2-methylfuran-3-carboxylate was increased to 0.762 and when longer reaction times (ca.

12 hr.) were used, the reported yield of 83% could be increased to 93%. Boiling points observed for the compound were 98-101°/29-30 mm. and 78°/10 mm. [lit. (45), b.p. 70°/7 mm.].

The n.m.r. spectrum (neat) of the compound showed adsorptions at 2.71 (1H, doublet, J = 1.9), 3.59 (1H, doublet, J = 1.9), 5.21 (1H, singlet), 5.63 (2H, singlet), and 7.83 τ (2H, singlet). The infrared spectrum of the compound showed λ_{max} 2.96, 3.38, 3.44, 6.14, 6.61, 8.78, 9.56, 10.02, 11.19, and 13.72 μ, among others.

2-Methyl-3-chloromethylfuran. This compound was prepared as described in the literature (45) and showed b.p. 55-59°/16 mm. (47% yield) [lit. (45), b.p. 57-59°/16 mm.].

Attempted Conversions of 2-Methyl-3-chloromethylfuran Into 2,3-Dimethylfuran. 2-Methyl-3-chloromethylfuran (15.5 g., 0.118 mole) was added to 120 ml. of 90% acetic acid that was contained in a 250-ml. three-necked round-bottomed flask fitted with a mechanical stirrer, an addition funnel, and a reflux condenser. Immediately after mixing the reactants, the resulting solution turned black, and in several minutes lumps of carbonaceous material appeared. Zinc dust (39 g., 0.597 mole) was added over a period of ca. 15 min., while stirring, and the stirring was continued overnight. The solution was boiled under reflux 3 hr. and then was poured into cold water (600 ml.). The solution was then extracted thoroughly with ether. The ether extract was dried and the ether was removed by distillation at atmospheric pressure using a short Vigreaux column. The residue consisted of a small quantity (ca. 250 mg.) of black tar and was discarded.

Magnesium (3 g., 0.123 atom) and 100 ml. of dry ether were placed

in a 250-ml. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an addition funnel, a reflux condenser, and a drying tube. A solution of 2-methyl-3-chloromethylfuran (16.0 g., 0.123 mole) in 25 ml. of dry ether was placed in the addition funnel and ca. 10 ml. of the solution was added dropwise while stirring. The mixture was then heated on the steam bath 30 min. and cooled; there was no evidence of reaction. Methyl iodide (ca. 0.2 ml.) was added, and the mixture began to boil spontaneously within several minutes. The remainder of the ether solution of 2-methyl-3-chloromethylfuran was then added dropwise to the reaction mixture. After the addition was complete, the mixture was boiled under reflux for 1 hr., cooled, and ca. 20 ml. of water was added. This was followed by the addition of sufficient 10% hydrochloric acid to dissolve most of the inorganic precipitate. The ether layer was separated, and the aqueous layer was extracted with 50 ml. of ether. The combined ether extract was dried, and the solvent was removed by distillation at atmospheric pressure. Distillation of the residue yielded ca. 2 g. of unidentified material, b.p. 65-70° at atmospheric pressure, which was not investigated further.

2,3-Dimethylfuran. A mixture of 119.0 g. (1.06 mole) of 2-methyl-3-hydroxymethylfuran, 105 g. (1.33 mole) of dry pyridine, and 335 ml. of dry ether was placed in a 1-l. three-necked round-bottomed flask fitted with a mechanical stirrer, an addition funnel, and an alcohol thermometer. The mixture was cooled to -5° in an ice-acetone bath, while stirring, and the addition of a solution of 139.0 g. (1.19 mole) of thionyl chloride in 120 ml. of pentane was begun at a moderate rate. When the temperature of the reaction mixture had increased to 20°, the rate of

addition was regulated so as to maintain that temperature. When the addition was complete, the supernatant liquid in the reaction flask was poured into a 2-l. separatory funnel, and the solid residue was dissolved in a solution of 40 ml. of concentrated hydrochloric acid in 200 ml. of water. The resulting solution was added slowly to the material in the separatory funnel; large quantities of sulfur dioxide were released. The reaction flask was then rinsed with 100 ml. of ether, which was added to the material in the separatory funnel. The aqueous layer was removed, extracted twice with 100-ml. portions of ether, and the combined ether extracts were dried for 1.5 hr. with anhydrous potassium carbonate. Anhydrous magnesium sulfate was then added, and the drying was continued for 0.5 hr. The drying agents were removed by filtration and the brown solution of 2-methyl-3-chloromethylfuran was concentrated to a volume of about 200 ml.

The above ether solution was added dropwise, while stirring, to a mixture of 33 g. (0.87 mole) of lithium aluminum hydride and 500 ml. of dry ether that was contained in a 2-l. three-necked flask fitted with an addition funnel, a mechanical stirrer, a reflux condenser, and a drying tube. The rate of addition of the ether solution of the 2-methyl-3-chloromethylfuran was regulated so as to maintain a moderate reflux. When the addition was complete, the mixture was stirred overnight. Water (50 ml.) was then added dropwise while stirring and cooling in an ice-acetone bath. When the addition was complete, a solution of 91.5 ml. of concentrated sulfuric acid in 400 ml. of water was added slowly while stirring and cooling; this was followed by the addition of 400 ml. of water. The mixture was then stirred at room temperature until all the inorganic material had dissolved. The aqueous layer was removed and

extracted with 100 ml. of ether. The combined ether solutions were washed with 100 ml. of 5% sodium hydroxide and then with 200 ml. of water. The ether solution was dried and the ether was removed by distillation using a lab-size spinning-band distillation column. The residue, after distillation through the same column, yielded 58.3 g. (57.2%) of 2,3-dimethylfuran, b.p. 94-95°/738.4 mm., $\eta_D^{24^\circ}$ 1.4411 [lit. (46), b.p. 90-91°/680 mm., $\eta_D^{20^\circ}$ 1.4452]. The n.m.r. spectrum of the compound (neat) showed absorptions at 2.91 (1H, doublet, J = 1.95; additional splitting of each component was present), 3.94 (1H, doublet, J = 1.95; additional splitting of each component was present), 7.93 (3H, closely spaced multiplet), and 8.16 τ (3H, closely spaced multiplet). The infrared spectrum of the compound showed λ_{max} 3.33, 6.10, 6.60, 6.86, 8.17, 8.80, 9.58, 10.64, and 11.16 μ, among others.

The intermediate 2-methyl-3-chloromethylfuran could be isolated as described (45); however, this compound decomposed rapidly at room temperature, and it was found that better overall yields of 2,3-dimethylfuran could be obtained when the isolation of the intermediate was not attempted.

Synthesis of 2,3-Dimethyl-2,5-dihydrofuran

cis- And trans-2,5-Dimethoxy-2,3-dimethyl-2,5-dihydrofuran. To 514 ml. of dry methanol contained in a 2-l. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, a drying tube, and an addition funnel was placed 85 g. (0.865 mole) of anhydrous potassium acetate and 39.3 g. (0.409 mole) of 2,3-dimethylfuran. The mixture was placed in a dry ice-acetone bath and was cooled to about -70° while stirring. A solution of 65.3 g. (0.408 mole) of bromine in 410 ml. of dry

methanol was then added (while stirring) at a rate such that the liquid stream just failed to break into drops. When the addition was complete, the dry ice-acetone bath was removed and the mixture was stirred for an additional 15 min. The mixture was then poured into 1.35 l. of saturated calcium chloride solution, and after mixing completely, the solution was extracted with four 200-ml. portions of ether. The combined ether extracts were washed with 200 ml. of a saturated solution of potassium carbonate and dried. The ether was removed by distillation at atmospheric pressure, and the residue was distilled *in vacuo*. This gave 54.45 g. (84%) of a mixture of *cis*- and *trans*-2,5-dimethoxy-2,3-dimethyl-2,5-dihydrofurans that showed b.p. 61-63°/15 mm. and $\eta_D^{24^\circ}$ 1.4352. The relative ratio of the *cis* to the *trans* isomer in the material that showed b.p. 61-63° was 66:34, respectively, as shown by integration of the n.m.r. spectrum. A portion of this mixture from another preparation was distilled using a micro spinning band column for elemental analysis and showed b.p. 61°/14.5 mm.

Anal.	$C_8H_{14}O_3$	Calc'd:	C, 60.72; H, 8.86
	(158.2)	Found :	C, 60.74; H, 9.13

The n.m.r. spectrum (neat) of the preparation showed absorptions for the *cis* isomer at 4.28-4.48 (1H, complex), 4.63-4.75 (1H, complex), 6.61 (3H, singlet), 6.94 (3H, singlet), 8.22-8.37 (3H, complex), and 8.66 τ (3H, singlet). The n.m.r. spectrum showed absorptions for the *trans* isomer at 4.28-4.48 (2H, complex), 6.70 (3H, singlet), 7.03 (3H, singlet), 8.22-8.37 (3H, complex), and 8.60 τ (3H, singlet).

The infrared spectrum (film) of the preparation showed λ_{max} 3.37, 5.97 (weak), 6.96, 7.32, 8.41, 8.59, 9.74, 10.56, 11.39, 12.06, and 12.78

μ, among others.

3-Methyl-4-oxo-cis-2-pentenal. A mixture of 10.0 g. (0.065 mole) of cis- and trans-2,5-dimethoxy-2,3-dimethyl-2,5-dihydrofuran and distilled water (54 ml.) was warmed to 60° on a steam bath, while swirling, and then was allowed to stand 12 hr. at room temperature. The mixture was then heated at 75° for 30 min., and the resulting cloudy, orange solution was cooled and extracted continuously with ether for 15 hr. The yellow ether extract was dried, and the ether was removed by distillation at atmospheric pressure. The orange residue was distilled in vacuo using a micro spinning band column with a pot temperature of 75°. This yielded 4.151 g. (58.4%) of 3-methyl-4-oxo-cis-2-pentenal b.p. 51°/1 mm. [lit. (47), b.p. 80-83°/2 mm.]. There was a considerable quantity of resinous, brown residue after the distillation was complete. The n.m.r. spectrum (neat) of the compound showed absorptions at 0.34 (1H, doublet, J = 7.2), 3.00 (1H, doublet, J = 7.2, each component of which was split into a quartet, J = 1.65), 7.61 (3H, singlet), and 7.83 τ (3H, doublet, J = 1.65). The infrared spectrum (film) showed λ_{max} 2.85 (weak), 3.39, 5.93, 6.21, 6.94, 7.37, 8.39, 8.70, and 10.69 μ, among others.

Preparation of 3-Methyl-cis-2-pentene-1,4-diol. One hundred grams (0.655 moles) of 2,5-dimethoxy-2,3-dimethyl-2,5-dihydrofuran was mixed with 554 ml. of distilled water, and the solution was allowed to stand, with occasional swirling, for 48 hr. at room temperature. At the end of this time, the solution was orange and cloudy. This solution was added dropwise, while stirring, to a solution, which had been cooled to 0°, of 15 g. (0.397 mole) of sodium borohydride dissolved in the minimum amount of distilled water. The rate of addition was controlled so that the

temperature of the solution remained below 1°. When the addition was complete, the solution was stirred overnight at room temperature. The solution was concentrated to 200 ml. and then was extracted continuously with methylene chloride for two days. The methylene chloride extract was dried, and the solvent was evaporated. Distillation of the residue *in vacuo* yielded 62.66 g. (85%) of 3-methyl-*cis*-2-pentene-1,4-diol that showed b.p. 92-94°/0.7 mm. A portion of the material was redistilled *in vacuo* for elemental analysis and showed b.p. 75°/0.25 mm., 86°/0.4 mm., and $\eta_D^{23°}$ 1.4374.

Anal.	$C_6H_{12}O_2$	Calc'd:	C, 62.04; H, 10.41
	(116.2)	Found :	C, 61.96; H, 10.53

The n.m.r. spectrum (40%, deuterium oxide) of the compound showed absorptions at 4.59 (1H, broad triplet, J = 7.5), 5.25 (1H, quartet, J = 7.0), 5.33 (HOD), 5.88 (2H, broad doublet, J = 7.5), 8.28 (3H, closely spaced multiplet), and 8.79 τ (3H, doublet, J = 7.0). The infrared spectrum (film) showed λ_{max} 2.90, 3.38, 6.10, 6.95, 7.30, 7.60, 8.30, 8.9-9.4, 10.24, and 11.70 μ, among others.

Attempted Cyclization of 3-Methyl-*cis*-2-pentene-1,4-diol. 3-Methyl-*trans*-2-pentenal. One and four-tenths grams of Dowex 50W-X8 ion-exchange resin in the hydrogen phase and 3.201 g. (28.4 mmoles) of 3-methyl-*cis*-2-pentene-1,4-diol were placed in a 10-ml. round-bottomed flask, and the flask was fitted with a distillation head and a condenser. The reaction vessel was placed in an oil bath and was heated slowly to 120°. Distillation then began, and the distillate was collected while the temperature of the oil bath was slowly raised to 160°. At this temperature, distillation ceased. The distillate was extracted with 30 ml. of ether. The

extract was dried, and the bulk of the ether was removed by distillation at atmospheric pressure. The tan residue yielded, upon distillation using a micro spinning-band distillation column, a small forerun of ether, which was followed by 2.540 g. (91.4%) of 3-methyl-trans-2-pentenal, b.p. 130-133°/743 mm. [lit. (48), b.p. 50-53°/12 mm.].

This compound yielded a 2,4-dinitrophenylhydrazone by the usual (40) method that after recrystallization from ethanol-ethyl acetate, had mp. 167-168° [lit. (48), m.p. 169-170°].

dl-2,3,5-Trideoxy-3-C-methyl-2,3-dibromoarabitol and dl-2,3,5-Trideoxy-3-C-methyl-2,3-dibromoxylitol. A solution of 56.1 g. (0.484 mole) of 3-methyl-cis-2-pentene-1,4-diol in 100 ml. of methylene chloride was placed in a 500-ml. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an addition funnel, and an alcohol thermometer. The mixture was cooled to 5°, and a solution of 78.5 g. (0.49 mole) of bromine in 75 ml. of methylene chloride was added, while stirring, at a rate that maintained a temperature of less than 10° throughout the addition. The reaction mixture became green soon after the addition was begun, and white crystalline material began to separate from the solution when the addition was ca. 2/3 complete. When the addition was complete, the solid material was filtered and was washed thoroughly with methylene chloride; this yielded 27.0 g. (22%) of material that showed m.p. 129-132°. A portion of this material was recrystallized from benzene-ethyl acetate for elemental analysis and showed m.p. 132-134.5°.

Anal.	$C_6H_{12}O_2Br_2$	Calc'd:	C, 26.12; H, 4.38; Br, 57.93
	(276.0)	Found :	C, 26.30; H, 4.47; Br, 58.26

The n.m.r. spectrum (saturated solution in pyridine) showed

absorptions at 3.29 (2H, singlet), 5.03 (1H, doublet of doublets, J = 4.5 and 7.0), 5.38 (1H, quartet, J = 6), 5.52-5.71 (2H, complex), 7.98 (3H, singlet), and 8.47 τ (3H, doublet, J = 6). The infrared spectrum (pellet) showed λ_{max} 2.84, 7.39, 8.24, 9.22, and 9.82 μ, among others.

2,3-Dimethyl-3,4-trans-dibromotetrahydrofurans. The green filtrate from above was concentrated to a thick sirup (bath temperature less than 30°) and placed in a 200-ml. round-bottomed flask that had been fitted with an apparatus for vacuum distillation. Dowex 50W-X8 ion-exchange resin, 25 g.) was then added and the mixture was heated to 125-135° in an oil bath under water aspirator vacuum. At this temperature, material that consisted of two phases distilled. When no more material distilled, 100 ml. of methylene chloride was added to the purple distillate, and the water layer was discarded. The methylene chloride solution was then washed with three 50-ml. portions of water and dried over magnesium sulfate-potassium carbonate. The solvent was evaporated from the tan solution, and the residue was distilled in vacuo. This yielded 46.4 g. (46.7%) of colorless liquid, b.p. 66°/3.0 mm. This material rapidly evolved hydrogen bromide and darkened when stored at room temperature, but could be stored for several days without change at -80°.

2,3-Dimethyl-2,5-dihydrofuran. A mixture of 40 g. (0.612 atom) of zinc dust and 35 ml. of n-hexyl alcohol was placed in a 125-ml. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an addition funnel, and an apparatus for distillation. The mixture was heated to 135°, while stirring. Heating was discontinued, and a solution of 40.58 g. (0.157 mole) of a mixture of 2,3-dimethyl-3,4-trans-dibromotetrahydrofurans was added so as to maintain a temperature of

135-140°. The crude 2,3-dimethyl-2,5-dihydrofuran distilled from the reaction mixture during the addition, and when the addition was complete, the mixture was distilled until the temperature of the distillate reached 160°. The entire distillate was dried and was distilled using a lab-size spinning-band column. The fraction that showed b.p. 60-110° was collected as crude 2,3-dimethyl-2,5-dihydrofuran and was dried and redistilled. This gave 12.0 g. (79.5%) of 2,3-dimethyl-2,5-dihydrofuran, b.p. 90-105° at atmospheric pressure. The n.m.r. spectrum (neat) of the crude 2,3-dimethyl-2,5-dihydrofuran of b.p. 90-105° showed the presence of approximately 5% 2,3-dimethylfuran. The 2,3-dimethylfuran in this preparation showed absorptions at 2.80 (1H, doublet, $\underline{J}$ = 2), 3.89 (1H, doublet, $\underline{J}$ = 2), 7.87 (3H, singlet), and 8.12 τ (3H, singlet). This material was combined with 12.0 g. of 2,3-dimethyl-2,5-dihydrofuran of similar purity. The combined product was distilled from calcium hydride using a lab-size spinning-band column and furnished 16.68 g. (56.1%, based on the total starting material used) of pure 2,3-dimethyl-2,5-dihydrofuran, b.p. 102° at atmospheric pressure, $\eta_D^{27^0}$ 1.4280 [lit. (49), b.p. 104° $\eta_D^{23^0}$ 1.4325].

A portion of the above material was redistilled for elemental analysis using a micro spinning band column and showed b.p. 102° at atmospheric pressure.

Anal.	$C_6H_{10}O$	Calc'd: C, 73.43; H, 10.27
	(98.1)	Found : C, 72.91; H, 10.45

The n.m.r. spectrum (20%, carbon tetrachloride) showed absorptions at 4.50-4.68 (1H, closely spaced multiplet), 5.20-5.67 (3H, complex), 8.32 (3H, closely spaced multiplet), and 8.83 τ (3H, doublet, $\underline{J}$ = 6.0). The infrared spectrum showed λ_{max} 3.37, 3.50, 6.02, 6.97, 7.37, 7.48, 9.21,

9.40, 9.77, 10.72, 11.60, 12.54, 12.85, and 14.72 μ, among others.

2,3-Dimethyl-2,5-dihydrofuran from Acetoin and Vinyltriphenylphosphonium Bromide

This compound was prepared by the published procedure (49) with the modification that the final reaction mixture was not poured into water and the product extracted with ether. Instead, the reaction mixture was distilled, and the distillate was collected until the temperature of the distilling vapor reached 150°. After redistillation using a lab-size spinning-band column the product showed b.p. 102-104° (42% yield) [lit. (49), b.p. 104°]. A fraction that showed b.p. 65-80° was also collected. The n.m.r. spectrum of this fraction showed it to consist predominantly of ethanol and benzene.

Several modified procedures, using the modified work-up described above, were tried in an attempt to improve the yield of 2,3-dimethyl-2,5-dihydrofuran and are described below. The modified procedures utilized the same molar ratios of the reactants as the published procedure.

Addition of a slurry of the sodium salt of acetoin to vinyltriphenylphosphonium bromide dissolved in the minimum amount of dimethylformamide resulted in an 8.2% yield of 2,3-dimethyl-2,5-dihydrofuran.

Addition of a solution of vinyltriphenylphosphonium bromide in the minimum amount of dimethylformamide to a slurry of the sodium salt of acetoin in ether, cooled in an ice bath, gave a 36.9% yield of 2,3-dimethyl-2,5-dihydrofuran.

Hydroxylation of 2,3-Dimethyl-2,5-dihydrofuran Using the Silver Acetate-Iodine-Wet Acetic Reagent. dl-4-Epidihydrodideoxystreptose

In a 500-ml. round-bottomed three-necked flask that had been fitted

with a mechanical stirrer, a reflux condenser, and a powder funnel was placed 232 ml. of redistilled glacial acetic acid, 19.112 g. (0.115 mole) of silver acetate and 5.00 g. (0.510 mole) of 2,3-dimethyl-2,5-dihydrofuran. Finely powdered iodine (13.60 g., 0.0535 mole) was added, while stirring, over a period of 0.5 hr. When the addition was complete, the mixture was stirred for 0.5 hr., and 22.95 ml. of aqueous acetic acid [4.00 g. of water per 100 ml. of solution, 0.918 g. of water (0.051 mole)] was then added. The resulting mixture was heated for 3.5 hr. at 60-65°. Solid sodium chloride (ca. 5 g.) was then added, and the solution was filtered. The inorganic material was washed thoroughly with hot benzene. The combined filtrates were concentrated to ca. 50 ml., filtered, and then concentrated to ca. 10 ml. The resulting solution was dissolved in 20 ml. of methanol and the pH of the solution was adjusted to 7.0 using methanolic potassium hydroxide (ca. 10%). Potassium hydroxide (4.2 g., 0.075 mole) dissolved in the minimum amount of methanol was then added, and the mixture was allowed to stand under nitrogen overnight. The solution was then neutralized with 1.5 N hydrochloric acid and most of the methanol was evaporated. The resulting dark solution was extracted continuously with chloroform for 6 hr. This yielded 2.431 g. of a viscous black sirup that resisted crystallization. This sirup was chromatographed over silicic acid (50 g.) using chloroform. Fraction 1 (265 ml.) contained 588 mg. of a black tar that was discarded. The eluting solvent was then changed to 2.0% methanol in chloroform. Fraction 2 (180 ml.) contained 288 mg. of black tar that was discarded. The eluting solvent was next changed to 3% methanol. Fraction 3 (360 ml.) contained 1.337 g. (19.8%) of a sirup that furnished crystalline material, m.p. 51-55°, from isopropyl

ether. Sublimation of the tan crystals at 45° and 80 μ furnished 963 mg. (14.3%) of hygroscopic white crystalline dl-4-epidihydrodideoxystreptose, m.p. 57-58°. A portion of this material was recrystallized three times from isopropyl ether for elemental analysis and showed m.p. 58.5-59.5° (sealed tube).

Anal.	$C_6H_{12}O_3$	Calc'd: C, 54.53; H, 9.15
	(132.2)	Found : C, 54.75; H, 8.95

The n.m.r. spectrum (7%, deuteriochloroform) showed absorptions at 5.89 (1H, a doublet, J = -10.00; each component of which split into a doublet, J = 3.25), 6.18 (1H, a doublet, J = 5.25; each component of which was split into a doublet, J = 3.25), 6.22 (1H, a quartet, J = 6.4), 6.35 (1H, a doublet, J = -10.00; each component of which split into a doublet, J = 5.25), 6.67 (2H, singlet), 8.85 (3H, singlet), and 8.85 τ (3H, doublet, J = 6.40). The infrared spectrum (10%, chloroform) of the compound showed λ_{max} 2.89, 3.32, 6.90, 7.25, 8.09, 8.75, 9.18, 9.87, 10.12, and 10.73 μ, among others.

GLC (10% QF-1, Argon Inlet Pressure 20 psig, C.T. 75°) analysis of the crude reaction product showed only one volatile component at R.T. 9.94 min. Under the same conditions synthetic dl-dihydrodideoxystreptose gave only one peak at R.T. 8.46 min.

Hydroxylation of 2,3-Dimethyl-2,5-dihydrofuran Using Osmium Tetroxide

2,3-Dimethyl-2,5-dihydrofuran (980 mg., 10.0 mmole) and 5.38 ml. (0.01 mole of hydrogen peroxide) of a 6.32% solution of hydrogen peroxide in t-butyl alcohol prepared as previously described (50) were placed in a 25-ml. round-bottomed flask. Osmium tetroxide (1 mg.) dissolved in 1 ml. of t-butyl alcohol was then added; the mixture immediately turned black

and became warm. After standing for 24 hr., the solvent was evaporated and 364 mg. (28.6%) of black sirup was obtained.

Quantitative analysis of the reaction product was performed by GLC (10% QF-1, A.I.P. 20 psig, C.T. 94°) analysis of a mixture of the crude product (25.8 mg.) and lauryl alcohol (7.4 mg.). This mixture showed peaks at R.T. 1.83 (area, 0.13 $in.^2$), 2.36 (area, 0.05 $in.^2$), 2.84 (area, 0.02 $in.^2$), 4.02 (area, 1.04 $in.^2$), 4.16 (area, 2.60 $in.^2$), 6.18 (area, 0.49 $in.^2$), 8.81 (area, 0.05 $in.^2$), 16.79 (area, 6.34 $in.^2$), and 24.61 min. (area, 0.16 $in.^2$). Under identical conditions lauryl alcohol showed only one peak at 16.79 min.; the crude product showed no peaks between 8.81 and 24.61 min. A mixture of dl-dihydrodideoxystreptose (44.8 mg.) and lauryl alcohol (46.3 mg.) was analyzed by GLC (same conditions as above) in order to determine the relative molar response of the two compounds and showed peaks at R.T. 4.02 (area, 1.88 $in.^2$) and 16.79 min. (area, 1.34 $in.^2$).

Hydroxylation of 2,3-Dimethyl-2,5-dihydrofuran Using Potassium Permanganate

A mixture of 16.00 g. (0.163 mole) of 2,3-dimethyl-2,5-dihydrofuran and 200 ml. of distilled water was placed in a 1-l. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an alcohol thermometer, and an addition funnel. The mixture was cooled to 1° in an ice-methanol bath and, while stirring, a solution of 25.8 g. (0.163 mole) of potassium permanganate in 500 ml. of distilled water was added at a rate that maintained a temperature of $1° \pm 1°$. When the addition was complete, the mixture was removed from the ice bath and was allowed to stand 1 hr. at room temperature. At the end of this time, the

mixture had set to a purple gel. The mixture was then heated on a steam bath for 1 hr., and during this time the color changed from purple to chocolate brown. The mixture was filtered using suction, and the insoluble material was triturated thoroughly with two 200-ml. portions of boiling water. The combined aqueous filtrate was concentrated to ca. 150 ml. and was extracted continuously with chloroform for 60 hr. This yielded 10.741 g. of a brown sirup that resisted crystallization. GLC analysis (10% QF-1, A.I.P. 20 psig, C.T. 78°) of the sirup showed peaks at R.T. 7.40 (area, 0.41 $in.^2$) and 8.80 min. (area, 1.40 $in.^2$). Under identical conditions, crystalline dl-dihydrodideoxystreptose from another preparation showed R.T. 7.40 min., and crystalline dl-4-epidihydrodideoxystreptose obtained as previously described (51) showed R.T. 8.80 min. Authentic L-dihydrodideoxystreptose had GLC behavior identical to that of dl-dihydrodideoxystreptose.

The sirup was chromatographed over silicic acid (200 g., column dimensions 4.8 x 21.0 cm.), using chloroform. Fractions 1-3 contained no material. The eluting solvent was then changed to 2.1% methanol in chloroform. Fractions 4-6 (500 ml. each) contained 367 mg. of an unidentified black gum that was shown by GLC analysis to contain none of the desired product. Fraction 7 (2.90 l.) contained 10.34 g. (48.5%) of an amber sirup that was shown by GLC analysis to consist only of dl-dihydrodideoxystreptose (22.6%) and dl-4-epidihydrodideoxystreptose (77.4%). Fraction 8 (500 ml.) contained no material. The n.m.r. spectrum (40%, chloroform) of the crude unchromatographed material showed absorptions at 5.42 (2H, broad singlet), 5.67-6.58 (4H, complex, partially resolved), 8.77 (3H, singlet), 8.78 (3H, doublet, J = 6.3), 8.83 (3H, doublet, J = 6.4), and

8.84 τ (3H, singlet).

dl-4-Epidihydrodideoxystreptose. Fractional crystallization of fraction 7 (10.34 g.) from above was performed by dissolving the entire quantity of material in 15 ml. of isopropyl ether. The solution was seeded with dl-4-epidihydrodideoxystreptose obtained crystalline as previously described (57). The crystalline material that separated from the solution after standing at 0° overnight was collected and was washed with 3 ml. of cold isopropyl ether. The filtrate was concentrated to 15 ml. and was seeded with dl-dihydrodideoxystreptose obtained crystalline from a similar preparation (the initial crystallization of dl-dihydrodideoxystreptose was accomplished by allowing a 50% isopropyl ether solution of the material in the filtrate from the first crop of dl-4-epidihydrodideoxystreptose to stand at 0° for four days). The crystalline material that separated from the solution was collected and was washed with 3 ml. of cold isopropyl ether. The filtrate was further concentrated and seeded again with dl-4-epidihydrodideoxystreptose.. When crystallization was complete (24 hr.), the second crop of dl-4-epidihydrodideoxystreptose was collected and was washed with 3 ml. of cold isopropyl ether. This method of fractional crystallization was continued, using the filtrate from each crop, until no additional quantity of either dl-dihydrodideoxystreptose or dl-4-epidihydrodideoxystreptose could be obtained from the filtrate by seeding (about 2 g. of this sirup remained). The entire quantity (about 6 g.) of dl-4-epidihydrodideoxystreptose obtained from the fractional crystallization was sublimed in vacuo at 50° and 80 μ. The resulting snow-white material was recrystallized three times from 10 ml. of isopropyl ether and furnished 4.692 g. (22.7% based on the amount of

2,3-dimethyl-2,5-dihydrofuran used in the hydroxylation of dl-4-epidihydrodideoxystreptose, m.p. 58.5-59.5° (sealed tube).

bis-p-Nitrobenzoyl derivative of dl-4-epidihydrodideoxystreptose. To a solution of dl-4-epidihydrodideoxystreptose (132 mg., 1.0 mmole) in 15 ml. of dry pyridine was added, in small portions, while swirling, 1.265 g. (6.0 mmole) of freshly recrystallized p-nitrobenzoyl chloride. The solution was allowed to stand 18 hr. at room temperature and was then heated on a steam bath for 1 hr. At the end of this time, the solution was cooled, and saturated sodium bicarbonate solution (50 ml.) was added. After standing 1 hr., the solution was extracted with three 30-ml. portions of chloroform. The combined chloroform extract was washed with 2% hydrochloric acid until the odor of pyridine could not be detected in the chloroform extract. The extract was dried, and the solvent was evaporated. This yielded 538 mg. of a mixture of red gum and crystalline material. This material was dissolved in 5 ml. of 2-butanone and the solution was concentrated to 2 ml. Methanol (5 ml.) was added and the mixture was allowed to stand overnight at 0°. This furnished 202 mg. of brown crystalline material, m.p. 168-171°. A second crop of 8 mg. was obtained from the material in the filtrate by crystallization from 1.0 ml. of methanol. A portion of the crystalline material (194 mg.) was chromatographed over aluminia (10 g., column dimensions 2.3 x 6.0 cm.), using chloroform. Fraction 1 (20 ml.) contained 172 mg. of pale yellow crystalline material. Fraction 2 (10 ml.) contained 3 mg. of pale yellow crystalline material. Fraction 3 (10 ml.) contained no material. Fractions 1 and 2 (175 mg., 40.7%) were combined and were recrystallized twice from benzene-methanol (1:2) for elemental analysis. The analytical sample showed m.p.

171.5-172°.

Anal. $C_{20}H_{18}N_2O_9$ (430.4) Calc'd: C, 55.82; H, 4.22; N, 6.51
Found : C, 56.04; H, 4.33; N, 6.46

The n.m.r. spectrum (23.6%, deuteriochloroform) showed absorptions centered at 1.89 (8H, complex, four major lines), 4.21 (1H, doublet, J = 5.2, each component split into a doublet, J = 2.2), 5.55 (1H, doublet, J = -11.5, each component split into a doublet, J = 5.2), 5.61 (1H, quartet, J = 6.4), 6.02 (1H, doublet, J = -11.5, each component split into a doublet, J = 2.2), 8.35 (3H, singlet), and 8.56 τ (3H, doublet, J = 6.4). The infrared spectrum (KBr pellet) showed λ_{max} 5.80, 6.23, 6.58, 7.43, 7.77, 8.21, 9.07, 9.90, 11.50, 11.74, 13.88, and 14.00 μ, among others.

dl-Dihydrodideoxystreptose. The entire amount (about 3.2 g.) of dl-dihydrodideoxystreptose obtained crystalline from the fractional crystallization previously described was sublimed *in vacuo* at 60° and 80 μ. This yielded 2.686 g. of white material that furnished 2.534 g. (11.7% based on the 2,3-dimethyl-2,5-dihydrofuran used in the hydroxylation) of dl-dihydrodideoxystreptose after recrystallization from 8 ml. of isopropyl ether. A portion of dl-dihydrodideoxystreptose of similar purity obtained in another preparation was recrystallized twice from isopropyl ether for elemental analysis. The analytical sample showed m.p. 62-62.2°.

Anal. $C_6H_{12}O_3$ (132.2) Calc'd: C, 54.53; H, 9.15
Found : C, 54.56; H, 9.10

The n.m.r. spectrum (7%, deuteriochloroform) showed absorptions at 5.98 (1H, a doublet, J = 7.00; each member split into a doublet, J = 4.90), 6.09 (1H, a doublet, J = -8.75; each member split into a doublet, J = 4.90), 6.34 (1H, a doublet, J = -8.75; each member split into a doublet,

J = 7.00), 6.36 (1H, quartet, J = 6.30), 6.98 (2H, singlet), 8.78 (3H, singlet), and 8.79 τ (3H, doublet, J = 6.30). The infrared spectrum (10%, chloroform) showed λ_{max} 2.87, 3.30, 6.95, 7.29, 8.15, 9.85, 10.76, and 11.56 μ, among others. The n.m.r. spectrum and the infrared spectrum of the synthetic dl-dihydrodideoxystreptose were both identical with the corresponding spectra obtained from a naturally derived* sample of L-dihydrodideoxystreptose.

bis-p-Nitrobenzoyl derivative of dl-dihydrodideoxystreptose. To a solution of dl-dihydrodideoxystreptose (132 mg., 1.0 mmole) in 15 ml. of dry pyridine was added, in small portions, while swirling, 1.265 g. (6.0 mmole) of freshly recrystallized p-nitrobenzoyl chloride. The solution was allowed to stand 18 hr. at room temperature and was then heated on the steam bath for 1 hr. At the end of this time, the solution was cooled, and saturated sodium bicarbonate solution (50 ml.) was added. After standing 1 hr., the solution was extracted with three 30-ml. portions of chloroform. The combined chloroform extract was washed with 2% hydrochloric acid until the odor of pyridine had disappeared. The extract was dried, and the solvent was evaporated. This yielded 455 mg. of a mixture of brown crystals and red gum. This mixture was dissolved in 5 ml. of hot benzene, and the solution was concentrated to 2 ml. Methanol (4 ml.) was added, and after standing at 0° overnight, 212 mg. of brown crystals separated from the solution. This material was collected and combined with a second crop of 21 mg. obtained by crystallization of the material in the filtrate from 1.5 ml. of methanol. The first crop showed m.p.

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* The author is very grateful to Mr. R. K. Chawla for this sample.

155-157°. Chromatography of the brown crystalline material (229 mg.) over aluminia (10 g., column dimensions 2.6 x 6.0 cm.) was performed using chloroform. Fraction 1 (20 ml.) contained 193 mg. of pale yellow crystalline material, fraction 2 contained 10 mg. of pale yellow crystalline material, and fraction 3 (10 ml.) contained no material. Fractions 1 and 2 (203 mg., 46.8%) were combined and recrystallized twice from benzene-methanol (1:2) for elemental analysis. The analytical sample showed m.p. 159.5-160.5°.

Anal.	$C_{20}H_{18}N_2O_9$	Calc'd:	C, 55.82; H, 4.22; N, 6.51
	(430.4)	Found :	C, 56.03; H, 4.36; N, 6.64

The n.m.r. spectrum (20%, deuteriochloroform) of the compound showed absorptions centered at 1.86 (8H, complex, four major lines), 4.24 (1H, doublet, J = 4.8; each component split into a doublet, J = 2.9), 5.70 (1H, doublet, J = -11.1; each component split into a doublet, J = 4.8), 5.72 (1H, quartet, J = 6.6), 5.88 (1H, doublet, J = -11.1; each component split into a doublet, J = 2.9), 8.16 (3H, singlet), and 8.50 τ (3H, doublet, J = 6.6). The infrared spectrum (KBr pellet) showed λ_{max} 5.81, 6.26, 6.59, 7.75, 8.22, 8.91, 9.12, 9.93, 11.50, 11.77, 12.77, and 13.99 μ, among others.

Attempted Optical Resolution of dl-Dihydrodideoxystreptose

3-Hydrogen Phthaloyl Derivative of 2-Methyl-2,3-butanediol. 2-Methyl-2,3-butanediol was prepared by catalytic reduction of 3-hydroxy-3-methyl-2-butanone. The product showed b.p. 77°/13.5 mm. [lit. (52), b.p. 75-76°/14 mm.]. Phthalic anhydride (1.233 g., 8.32 mmole) was added to a solution of 1.00 g. (9.6 mmole) of 2-methyl-2,3-butanediol in 10.0 ml. of pyridine. The solution was heated on the steam bath for 1 hr. and was then poured into 50 ml. of distilled water. The pH of the solution was

adjusted to 1.0 with 2% hydrochloric acid. The solution was extracted with three 50-ml. portions of chloroform; the combined chloroform extract was dried, and the solvent was evaporated. This yielded 1.558 g. (92.6%) of crystalline material that showed m.p. 128-129°. Recrystallization of the product from the minimum amount of benzene yielded 1.242 g. (74%) of the 3-hydrogen phthaloyl derivative of 2-methyl-2,3-butanediol, which showed m.p. 128-129°. A portion of this material was recrystallized three times from benzene for elemental analysis. The analytical sample showed m.p. 131.5-132°.

Anal. $C_{13}H_{16}O_5$ (252.3) Calc'd: C, 61.90; H, 6.39
Found : C, 62.38; H, 6.42

The n.m.r. spectrum (20%, deuteriochloroform) of the compound showed absorptions at 1.32 (2H, broad singlet), 2.00-2.58 (4H, complex), 4.74 (1H, quartet, J = 6.5), 8.70 (6H, singlet), and 8.70 τ (3H, doublet, J = 6.5). The infrared spectrum (KBr pellet) of the compound showed λ_{max} 2.86, 3.36, 5.66, 5.81, 6.90, 8.32, 8.84, 9.14, 9.72, 10.72, 10.91, and 11.94 μ, among others.

Attempted Preparation of the 2-Hydrogen Phthaloyl Derivative of dl-Dihydrodideoxystreptose. To a solution of dl-dihydrodideoxystreptose (500 mg., 3.79 mmole) in 15 ml. of dry pyridine, 561 mg. (3.79 mmole) of freshly recrystallized phthalic anhydride was added. The mixture was heated on a steam bath under reflux for 18 hr., cooled, and poured into 40 ml. of water. Solid sodium bicarbonate (ca. 5 g.) was then added. After standing 1 hr., the solution was extracted with chloroform until the odor of pyridine had disappeared. The pH of the solution was adjusted to 1.0 using 5% hydrochloric acid, and the solution was extracted continuously

with chloroform for 5 hr. The extract was dried, and the solvent was evaporated. This yielded 790 mg. (76.4%) of a tan glass that resisted crystallization from a variety of solvents. The entire amount of material was chromatographed over silicic acid (20 g.) using chloroform. Fraction 1 (50 ml.) contained no material. Fraction 2 (45 ml.) contained 145 mg. of a sirup that contained crystalline material. Fraction 3 (85 ml.) contained 105 mg. of a brown glass. Fraction 4 (60 ml.) contained 107 mg. of a brown glass. The eluting solvent was then changed to 2% methanol in chloroform. Fraction 5 (100 ml.) contained 212 mg. of a brown glass. Fraction 6 (100 ml.) contained 112 mg. of a brown glass. Fraction 7 contained no material. Fractions 3-6 resisted crystallization from a variety of solvents. Fraction 2 was recrystallized from the minimum amount of isopropyl ether and furnished 80 mg. of material that showed m.p. 115-117°. A portion of this material was recrystallized three times from isopropyl ether for elemental analysis. The analytical sample showed m.p. 116.5-117.5°.

Anal.	$C_{14}H_{14}O_5$	Calc'd: C, 64.12; H, 5.38
	(262.3)	Found : C, 64.34; H, 5.44

The n.m.r. spectrum (29%, deuteriochloroform) showed absorptions at 2.10-2.40 (4H, complex), 5.18 (1H, doublet, J = 3.25), 5.85 (1H, doublet, J = -11.3), 6.35 (1H, doublet, J = -11.3; each component split into a doublet, J = 3.25), 6.45 (1H, quartet, J = 6.31), 8.38 (3H, singlet), and 8.68 τ (3H, doublet, J = 6.31). The infrared spectrum (KBr pellet) showed λ_{max} 3.31, 5.62, 5.82, 7.38, 7.60, 8.19, 8.84, 9.04, 11.57, 11.95, 13.12, 13.79, and 14.56 μ, among others. When the infrared spectrum of the compound was determined using a film of the uncrystallized material,

only one carbonyl absorption (5.60 μ) was observed.

The n.m.r. spectrum (17%, deuteriochloroform) of fraction 5 showed absorptions at 2.28-2.85 (11 squares, complex), 3.96 (5.7 squares, broad singlet), 4.84 (1H, broad triplet, J = 6), 5.88-6.68 (11.4 squares, partially resolved complex signal), 8.45 (1 square, singlet), and 8.58-9.00 (19.7 squares, four lines). The infrared spectrum (film) showed λ_{max} 2.80, 3.30, 3.70, 4.36, 5.59, 5.77, 6.24, 6.33, 6.90, 7.79, 8.94, 11.02, and 13.11 μ, among others.

Fractions 4 and 5 were combined with corresponding fractions from a similar preparation; a total of 488 mg. (1.74 mmole, assuming the material consisted of only the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose) of material was obtained. This material was dissolved in 1 ml. of acetone and 343 mg. (0.87 mmole, one-half of the calculated amount) of brucine dissolved in the minimum amount of hot acetone was added. This preparation resisted crystallization from a variety of solvents. Brucine (343 mg., 0.87 mmole) was then added to the solution of the preparation in 10 ml. of acetone, and the mixture was warmed to dissolve the brucine. This preparation also resisted crystallization from a variety of solvents.

An attempted preparation of the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose similar to the one described above was carried out. The pyridine solution of the reactant was not heated, but was allowed to stand at room temperature for nine days. Work up of the reaction mixture using the procedure described above, followed by chromatography of the product over silicic acid, gave results essentially identical to those obtained when the pyridine solution was heated.

The 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose

was recovered from the gummy brucine salt using the method previously described (53) for recovery of the bis-hydrogen phthaloyl derivative of dl-3-nordihydrodideoxystreptose.

Thin-layer chromatography (TLC) of the recovered 2-hydrogen phthaloyl derivative over silica gel HF_{254} (360 mμ) visualized under long wavelength U.V. light, using benzene-methanol-acetic acid (50:4:2) showed five spots at R_F 0.305 (weak), 0.389 (strong), 0.59 (strong), 0.76 (weak), and 0.824 (weak). Under identical conditions phthalic acid showed R_F 0.3 and the crystalline by-product of the attempted 2-hydrogen phthaloyl derivative preparation showed R_F 0.59.

A solution of dl-dihydrodideoxystreptose (205 mg., 1.52 mmole), pyridine (5 ml.), and phthalic anhydride (230 mg., 1.55 mmole) was boiled under reflux for 14 hr.; the solution was protected from moisture using a drying tube. The pyridine was evaporated *in vacuo* from the reaction mixture and the residue was dried *in vacuo* to constant weight at room temperature. There resulted 416 mg. (105%) of a tan glass. TLC analysis (silica gel HF_{254}; benzene-methanol-acetic acid, 50:4:2; 2 developments) showed spots at R_F 0.3 (weak, phthalic acid), 0.39 (strong, 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose), 0.59 (strong, crystalline by-product), 0.77 (weak, unknown), and 0.82 (weak, unknown).

Preparative TLC of the reaction product was performed using the same conditions as above, and the absorbant containing the band corresponding to the above band at R_F 0.39 was removed from the plate. The adsorbant was rinsed with eight 25-ml. portions of chloroform. The chloroform was evaporated; this yielded 6 mg. of material that showed spots, upon TLC analysis using the same conditions as above, at R_F 0.39 and 0.96.

Continuous extraction of the adsorbant with chloroform for three hours furnished 13 mg. of material that showed three spots, upon TLC analysis using identical conditions as above, at R_F 0.39, 0.65, and 0.96.

A portion (815 mg.) of the reaction product from an attempted phthalate preparation that showed spots at R_F 0.3, 0.39, 0.59, 0.77, and 0.82 was heated under reflux for four days with 25 ml. of acetic acid-chloroform (5:95). The chloroform-acetic acid solution was then evaporated. TLC analysis of the residue showed spots at R_F 0.30, 0.39, 0.59, 0.77, and 0.82. The spot at R_F 0.39 was less intense than it was in the material that had not been treated with hot acetic acid-chloroform.

l-Menthoxyacetyl Derivative of L-Dihydrodideoxystreptose. To a a solution of L-dihydrodideoxystreptose derived from streptomycin (63 mg., 0.476 mmole) in 5 ml. of dry benzene containing 50 mg. of dry pyridine, 107.8 mg. (0.474 mmole) of freshly distilled l-menthoxyacetyl chloride prepared as described elsewhere (44), was added dropwise while stirring and cooling. The mixture was stirred overnight, and 10 ml. of benzene was then added. The resulting benzene solution was washed with two 10-ml. portions of water, one 5-ml. portion of 1 N hydrochloric acid, one 5-ml. portion of 5% sodium bicarbonate solution, and finally with one 5-ml. portion of water. The benzene solution was dried, and the solvent was evaporated. This yielded 114 mg. (73%) of partially crystalline material that showed m.p. 41-58°. The material was chromatographed over silicic acid (2.3 g.) using chloroform. Fraction 1 (15 ml.) contained 7 mg. of material that was discarded. Fraction 2 (46 ml.) contained 24 mg. of brown sirup that was not investigated further. Fraction 3 (12 ml.) contained 67 mg. of crystalline material that showed m.p. 76-78°. Fraction 4 (24 ml.)

contained 12 mg. of material that was not investigated further. The l-menthoxyacetyl derivative of L-dihydrodideoxystreptose (fraction 3) showed $[\alpha]_D^{28^\circ}$ -56.02° ± 0.73 (c 3.32, 95% ethanol).

2-l-Methoxyacetyl Derivative of dl-Dihydrodideoxystreptose. dl-Dihydrodideoxystreptose (0.762 g., 5.77 mmole) was added to a solution of dry pyridine (0.510 g., 6.62 mmole) in 35 ml. of dry benzene; the mixture was warmed slightly to dissolve the solid. This mixture was cooled to 10° in an ice bath, while stirring, and a solution of freshly distilled l-menthoxyacetyl chloride (1.345 g., 5.77 mmole) in 25 ml. of dry benzene was added dropwise by means of an addition funnel that had been fitted with a drying tube. The temperature of the reaction mixture was maintained below 10°. When the addition was complete, the mixture was removed from the ice bath and was stirred overnight. The mixture was then washed successively with two 50-ml. portions of water, two 25-ml. portions of 0.1 N hydrochloric acid, two 50-ml. portions of 5% sodium bicarbonate solution, and two 50-ml. portions of water. The resulting benzene solution was dried, and the solvent was evaporated; this yielded 1.690 g. (87.5%) of a colorless sirup that crystallized within five minutes to give material that had m.p. 79-85°, $[\alpha]_D^{28}$ = -63.18° ± 0.97° (c 3.31 in 95% ethanol). A portion of the material was recrystallized three times from ligroin for elemental analysis and showed m.p. 85-86°.

Anal.	$C_{18}H_{32}O_5$	Calc'd: C, 65.82; H, 9.82
	(328.5)	Found : C, 66.06; H, 9.90

The infrared spectrum (5%, chloroform) showed λ_{max} 2.69, 3.35, 5.67, 6.89, 7.78, 8.90, 10.99, 11.54, and 11.89 μ, among others. In addition to showing λ_{max} at the positions described above, the infrared spectrum

showed an additional absorption at 5.81 μ when taken using a KBr pellet.

Attempted fractional crystallization. The mixture of the l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose (1.475 g.) from a preparation similar to that described above that showed $[\alpha]_D^{28}$ -63.42 ± 0.75° (c 3.34, 95% ethanol) was recrystallized from 25 ml. of ligroin and furnished 795 mg. of material that showed $[\alpha]_D$ -62.10 ± 0.3° (c 3.34, 95% ethanol). This material was recrystallized from 13 ml. of ligroin and furnished 412 mg. of material that showed $[\alpha]_D^{28}$ -63.39 ± 0.67° (c 3.34, 95% ethanol).

Attempted separation using counter-current distribution. The distribution coefficient for the mixture of l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose in the solvent system benzene-methanol-water (20:11:2) was found to be 0.49 for the top to bottom phase. The composition of the top phase was shown to be 1.6:4.0:1.0 by volume of benzene-methanol-water and the composition of the bottom phase was shown to be 10.0:5.5:1.0 by volume of benzene-methanol-water. The composition of each phase was determined by integration of the n.m.r. spectra of the two phases. The distribution coefficient was determined by dissolving 154.7 mg. of material in a mixture of 36.0 ml. of bottom phase, adding 28.8 ml. of top phase, and shaking thoroughly to equilibrate the material between the two phases. The two phases were then separated, and after evaporation of solvent it was found that 28.8 ml. of the top phase contained 44.0 mg. of material and 36.0 ml. of the bottom phase contained 112.0 mg. of material. The amount of material contained in a milliliter of each phase was then calculated, and from this the distribution coefficient was calculated.

The immiscibility of the solvent system methanol-petroleum ether (25:63) was found to be too sensitive to temperature changes to be used, although at 25° the distribution coefficient for top to bottom phase was found to be 0.473. A change of ± 5° was found to greatly change the amount of each phase present in this system.

The solvent system methanol-chloroform-water (14:20:6) was tried and was found to form an emulsion when shaken that was difficult to separate when the l-menthoxyacetyl derivatives were present. This solvent system was not investigated further.

Using the solvent system benzene-methanol-water (20:11:2) the countercurrent distribution apparatus was adjusted so that each transfer delivered 15 ml. of the moving (top) phase and four transfers (60 ml.) were collected in a fraction collector as one fraction. The mixture of l-menthoxyacetyl derivatives (2.06 g.) of dl-dihydrodideoxystreptose was dissolved in 30 ml. of bottom phase, and this solution was divided into three equal parts and placed in the first three cells. The reservoir was then filled with top phase that had been equilibrated with bottom phase, and the instrument was started. The fractions taken are summarized in the figure below.

Fractions 67-72 were combined (128.5 mg.) and chromatographed over silicic acid (2.30 g.) using chloroform. Fraction 1 (10 ml.) contained 6 mg. of material that was discarded. Fraction 2 (20 ml.) contained 95 mg. of crystalline material that showed $[\alpha]_D$ -61.34° ± 0.45° (c 3.1, 95% ethanol).

Fractions 79-81 (195 mg.) were combined and chromatographed over silicic acid (4.0 g.) using chloroform. Fraction 1 (20 ml.) contained

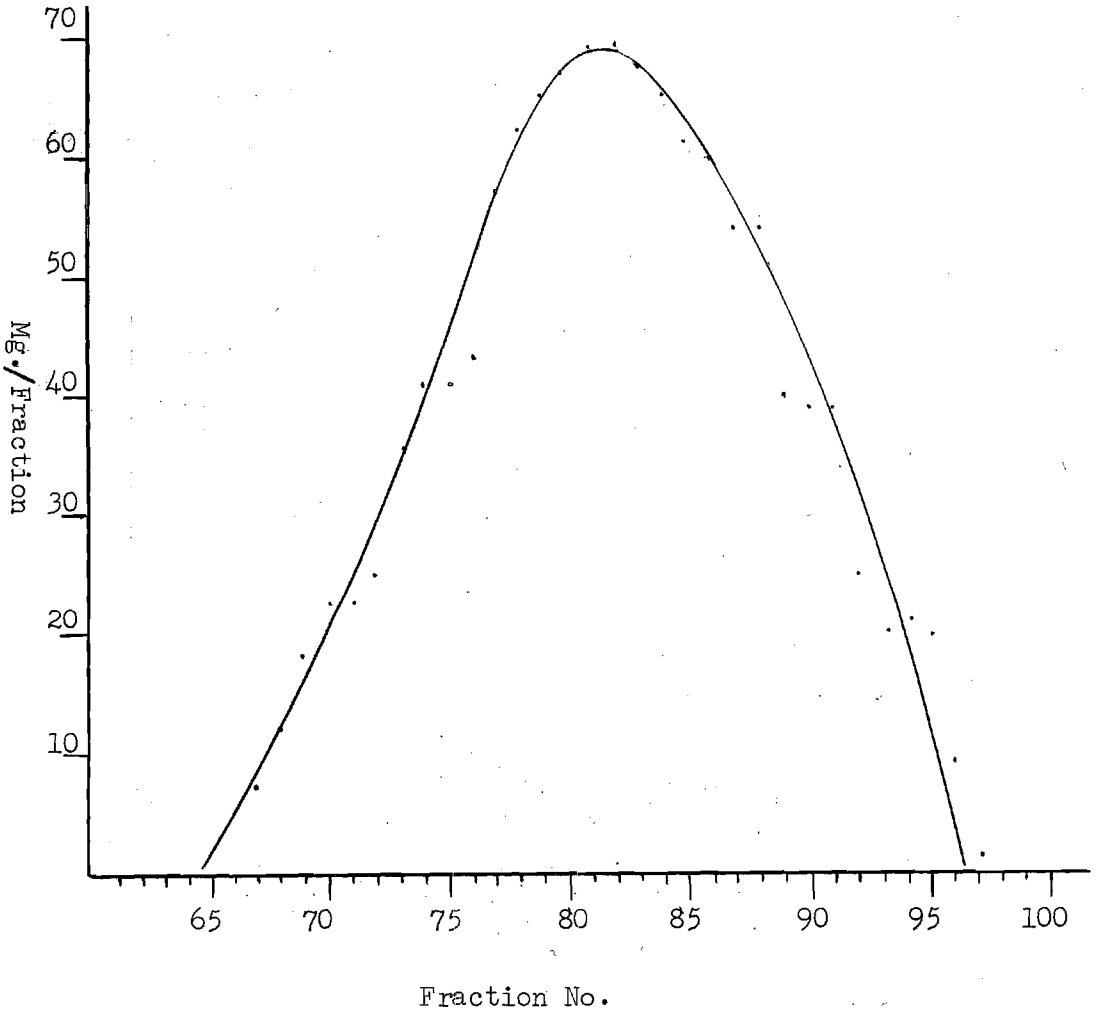


Figure 1. The Elution Pattern for the Attempted Separation of the l-Menthoxyacetyl Derivatives of dl-Dihydrodideoxystreptose Using Countercurrent Distribution.

17.3 mg. of brown oil that was discarded. Fraction 2 (32 ml.) contained 136 mg. of crystalline material that showed $[\alpha]_D$ -62.18° ± 0.31° (c 3.2, 95% ethanol.

Fractions 92-99 (127 mg.) were combined and chromatographed over silicic acid (3.0 g.) using chloroform. Fraction 1 (30 ml.) contained 33 mg. of brown oil that was discarded. Fraction 2 (42 ml.) contained 62 mg. of crystalline material that showed $[\alpha]_D^{29}$ -61.01° ± 0.8° (c 2.9, 95%

ethanol).

The contents of cells 164-199 in the countercurrent distribution apparatus were next combined, and contained 136 mg. of chloroform-soluble material that resisted crystallization and was not investigated further. The contents of cells 153-163 furnished 9.9 mg. of material, cells 142-152 furnished 21 mg. of material, cells 131-141 furnished 18 mg. of material, cells 120-130 contained 14 mg. of material, cells 109-119 contained 19 mg. of material, and cells 99-108 contained 16 mg. of material. The contents of these cells were brown oils that resisted crystallization and were not investigated further.

The countercurrent distribution fractions (123-128 and 132-141), that contained crystalline material but had not been chromatographed over silicic acid were combined with the crystalline silicic acid chromatography fractions from the three previously described silicic acid columns and this material (1.089 g.) was chromatographed over silicic acid (20 g.) using chloroform. Fraction 1 (80 ml.) contained 192 mg. of brown oil that was discarded. Fraction 2 (180 ml.) contained 823 mg. of crystalline material that showed $[\alpha]_D$ -59.78° ± 0.6° (c 2.004, 95% ethanol). Fraction 3 (100 ml.) contained 6 mg. of material that was discarded. A portion of fraction 2 (790 mg.) was recrystallized from ethanol-water and furnished 575 mg. of material that showed $[\alpha]_D$ -60.46° ± 0.7° (c 2.004, 95% ethanol). This material (575 mg.) was recrystallized from ethanol-water again and furnished 274 mg. of material that showed $[\alpha]_D$ -61.18° ± 0.3° (c 2.03, 95% ethanol). This 274 mg. of material was recrystallized from methanol at -80° and there was obtained 101 mg. of material that showed $[\alpha]_D$ -60.52° ± 0.39° (c 2.049, 95% ethanol).

All the filtrates and crystalline material from the attempted fractional crystallization of silicic acid chromatography of fraction 2 were combined; the material amounted to 766 mg. of the 2-l-menthoxyacetyl derivative of dl-dihydrodideoxystreptose.

This material (766 mg., 2.31 mmole) was hydrolyzed by allowing it to stand overnight in 20 ml. of methanol-water containing 200 mg. of sodium hydroxide. Continuous extraction of the hydrolysate with chloroform overnight yielded an extract that, after drying and evaporation of solvent, furnished 214.2 mg. (69.5%) of dl-dihydrodideoxystreptose that showed $[\alpha]_D$ $+0.197 \pm 0.59^0$ (c 1.01, chloroform) and m.p. 61.5-62° after two recrystallizations from isopropyl ether.

Attempted Separation Using GLC. GLC (11%, EGSS-X, A.I.P. 20 psig., C.T. 185°) analysis of the l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose showed only one symmetrical peak (R.T. 44.9 min.). Using 10% QF-1 (A.I.P. 20 psig., C.T. 189°) the l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose showed only one symmetrical peak at R.T. 44.65 min.

The trimethylsilyl derivatives of the 2-l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose were prepared (54) by mixing 10 mg. of the 2-l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose, 1.0 ml. of dry pyridine, 0.2 ml. of hexamethyldisilazane and 0.1 ml. of chlorotrimethylsilane in a small vial and shaking the solution for one minute. GLC analysis (3%, SE-30, A.I.P. 20 psig., C.T. 186°) of the mixture after 2 hr. showed peaks at R.T. 3.35 min. and 5.72 min. of approximately equal intensity. Under identical conditions the l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose showed one peak at R.T. 3.35 min. After

12 hr. GLC analysis of the mixture (under identical conditions) showed only one symmetrical peak at R.T. 5.72 min.

Using 10% QF-1 (A.I.P. 20 psig., C.T. 158°) the trimethylsilyl derivatives showed only one symmetrical peak at R.T. 42.2 min.

d-Bornyloxyacetyl Chloride. Stock d-borneol that showed $[\alpha]_D^{28}$ 32.52° (c 5.9, toluene) [lit. (55), $[\alpha]_D$ 37.6°, (c 5.9, toluene)] was converted into optically impure d-bornyloxyacetic acid in 80% yield using the published (55) procedure. Recrystallization of 2.041 g. of the acid from 5.0 ml. of hexane furnished 1.124 g. of material that showed $[\alpha]_D^{26}$ 46.00 ± 0.3° (c 2.0, 95% ethanol), and m.p. 72-74.5° [lit. (55), $[\alpha]_D$ 59.1° (c 2.0, 95% ethanol)]. The optically impure d-bornyloxyacetic acid was converted into d-bornyloxyacetyl chloride (95% yield) using the published (55) procedure. The acid chloride showed b.p. 88-89°/1.0 mm.

Stock d-borneol (67.4 g., 0.438 mole) was placed in a 2-l. three-necked round-bottomed flask that had been fitted with a mechanical stirrer, an addition funnel, and a reflux condenser. A solution of pyridine (40.0 g., 0.506 mole) in dry benzene (500 ml.) was added, and after the d-borneol dissolved, the resulting solution was cooled to 10°. A solution of 99.4 g. (0.432 mole) of optically impure d-bornyloxyacetyl chloride in 200 ml. of dry benzene was added dropwise, while stirring and cooling. When the addition was complete, the mixture was stirred overnight at room temperature. Water (300 ml.) was then added to dissolve the precipitated pyridine hydrochloride, and after removal of the water layer, the resulting benzene solution was washed with two 200-ml. portions of 2 N hydrochloric acid, two 100-ml. portions of 10% sodium bicarbonate solution, and finally with two 200-ml. portions of water. The bulk of the benzene

in the resulting material was steam distilled to remove the unreacted d-borneol. The residue was then dissolved in 900 ml. of ether, the ether solution was dried, and the solvent was evaporated. This furnished 146.4 g. (100%) of d-bornyl-d-bornyloxyacetate that showed $[\alpha]_D$ 52.40° ± 0.6° (c 2.0, chloroform) and m.p. 68-71° [lit. (55), m.p. 72°, $[\alpha]_D$ 63.3° (c 2.0, chloroform)].

The entire amount of ester from above was recrystallized from 100 ml. of methanol-water (100:8), collected on a filter, and washed with 100 ml. of ice cold methanol. The resulting material showed m.p. 72.5-73.5° and $[\alpha]_D$ 58.3° ± 0.5° (c 2.0, chloroform). The material was recrystallized from 100 ml. of methanol; the crystalline material that separated showed $[\alpha]_D$ 59.8° ± 0.5° (c 2.0, chloroform). Recrystallization of the resulting ester from 100 ml. of methanol furnished material that showed $[\alpha]_D$ 63.4° ± 0.7° (c 2.0, chloroform). This material was recrystallized again from 100 ml. methanol and 84.6 g. (57.8%) of optically pure d-bornyl-d-bornyloxyacetate that showed m.p. 72.8-73.2° and $[\alpha]_D$ 62.6° ± 1.0° (c 2.0, chloroform) was obtained.

The optically pure ester (84.6 g., 0.243 mole) was heated under reflux for 1.5 hr. with potassium hydroxide (16.4 g., 0.292 mole) dissolved in 1.62 l. of 95% ethanol. About 700 ml. of ethanol was then distilled from the solution at atmospheric pressure, and the remainder of the ethanol was removed by passing steam through the mixture. The resulting aqueous solution that contained solid d-borneol was extracted with four 350-ml. portions of ether. The ether extract was washed with three 200-ml. portions of water and was dried. Evaporation of the ether furnished 36.2 g. (95%) of d-borneol that showed m.p. 204.5-205.5° (sealed

tube) and $[\alpha]_D^{22}$ 40.40° ± 0.5° (c 5.94, toluene) [lit. (55) m.p. 204.5-205°, $[\alpha]_D$ 37.6° (c 5.9, toluene)].

The pH of the aqueous solution from the ether extraction was adjusted to 1.0 with 6 N hydrochloric acid, and the resulting mixture was extracted with three 500-ml. portions of ether. The ether extract was dried, and the solvent was evaporated. This yielded 51.20 g. (99%) of optically pure d-bornyloxyacetic acid. A portion of this material was recrystallized from hexane and showed m.p. 77.5-78° and $[\alpha]_D$ 55.11° ± 0.5° (c 2.0, 95% ethanol).

Recrystallized d-bornyloxyacetic acid (24.27 g., 0.105 mole) was heated at 60° for 3 hr. with 50 ml. of thionyl chloride. At the end of this time the excess thionyl chloride was removed by distillation *in vacuo*, and the residue was distilled *in vacuo*. This yielded 23.43 g. (97%) of d-bornyloxyacetyl chloride that showed b.p. 88-89°/1.0 mm. [lit. (55), b.p. 140-143°/17 mm.].

Attempted Preparation of the d-Bornyloxyacetyl Derivatives of dl-Dihydrodideoxystreptose. dl-Dihydrodideoxystreptose (103 mg., 0.78 mmole) was dissolved in a solution of dry pyridine (70 mg., 0.89 mmole) in dry benzene (10 ml.). The mixture was cooled in an ice bath and a solution of d-bornyloxyacetyl chloride (185 mg., 0.80 mmole) in benzene (15 ml.) was added dropwise while stirring. When the addition was complete the mixture was allowed to stand overnight, and then benzene (25 ml.) was added. The benzene solution was washed with three 15-ml. portions of water and was dried. The solvent was evaporated; this yielded 182 mg. (71.5%) of a sirup that resisted crystallization from a variety of solvents. This sirup was chromatographed over silicic acid (5.0 g.) using chloroform.

Fraction 1 (20 ml.) contained no material. Fraction 2 (15 ml.) contained 56 mg. of a colorless sirup. Fraction 3 (10 ml.) contained 66 mg. of a colorless sirup. Fraction 4 (6 ml.) contained 30 mg. of a colorless sirup. Fraction 5 (10 ml.) contained no material. The contents of fractions 2-4 resisted crystallization from a variety of solvents.

The infrared spectrum (film) of fraction 3 showed λ_{max} 2.81, 3.35, 5.70, 6.95, 8.92, 9.82, and 11.55 μ, among others.

Attempted Preparation of the Acid Chloride of l-Menthyl Hydrogen Phthalate. l-Menthol (15.6 g., 0.10 mole) was added to a solution of freshly recrystallized phthalic anhydride (14.8 g., 0.10 mole) in dry pyridine (100 ml.). The solution was boiled under reflux overnight. The solution was cooled, and the bulk of the pyridine was evaporated. The resulting brown sirup that contained crystalline material was dissolved in benzene (300 ml.). The benzene solution was washed with 5% hydrochloric acid until the odor of pyridine had disappeared. The benzene solution was dried and the solvent was evaporated. The crystalline residue was recrystallized from 150 ml. of ligroin two times. This furnished 20.10 g. (66%) of l-menthyl hydrogen phthalate that showed m.p. 111-113° [lit. (56), labile form m.p. 110°, stable form m.p. 122°]. The solvent was evaporated from the combined filtrates of the two recrystallizations. This yielded 11.62 g. of material that crystallized when cooled.

l-Menthyl hydrogen phthalate (2.048 g., 6.73 mmole) was dissolved in thionyl chloride (5 ml.). The solution was allowed to stand 6 hr. and then the thionyl chloride was evaporated *in vacuo* at room temperature. The resulting brown liquid that contained crystalline material was filtered and the crystalline material (753 mg.) was collected. This material

was identified as phthalic anhydride by its infrared spectrum, which was identical to the spectrum of an authentic sample. The filtrate contained 1.219 g. of a brown liquid that evolved hydrogen chloride while standing at room temperature. This material was not investigated further.

Attempted Preparation of the Acid Chloride of l-Menthyl Hydrogen Succinate. A solution of 10.06 g. (0.1 mole) of succinic anhydride and 15.6 g. (0.1 mole) of l-menthol in 120 ml. of dry pyridine was heated on the steam bath for 12 hrs. Most of the pyridine was then evaporated *in vacuo*, and the residue was dissolved in 200 ml. of benzene. The resulting benzene solution was washed with 5% hydrochloric acid until the odor of pyridine had disappeared. The solution was dried, and the solvent was evaporated. The crystalline material that resulted was recrystallized three times from ligroin. This yielded 11.64 g. (45.3%) of l-menthyl hydrogen succinate that showed m.p. 63.2-64° [lit. (57) m.p. 57-59°]. The product was very soluble in ligroin, and the combined filtrates from the recrystallizations contained 13.76 g. of l-menthyl hydrogen succinate that crystallized after evaporation of the solvent.

A solution of 10.00 g. (0.0391 mole) of l-menthyl hydrogen succinate in 15 ml. of thionyl chloride was heated at 35° for 3 hr. The excess thionyl chloride was evaporated at room temperature *in vacuo*. Attempted distillation of the resulting brown liquid at 0.2 mm. resulted in extensive decomposition of the material and the formation of succinic anhydride and hydrogen chloride.

After evaporation of excess thionyl chloride, the crude reaction product (3.10 g., 1.21 mmole) from a similar preparation was dissolved in 10 ml. of ligroin, centrifuged, and the supernatant liquid was removed

from the small amount (ca. 30 mg.) of succinic anhydride present. The petroleum ether solution was placed in a dry ice-acetone bath; crystalline material separated from the solution. The supernatant liquid was removed using a filter stick, and the resulting solid material was recrystallized three times from 25 ml. of petroleum ether in this way. The crystalline material (1.54 g., 46.4%) from the final recrystallization melted at about 30°. This material slowly evolved hydrogen chloride as it melted. The material was frozen in a dry ice-acetone bath and was dried in vacuo. The material melted during the drying, and after 25 min. of drying the material was found to be predominantly crystalline succinic anhydride.

Attempted Optical Resolution of dl-4-Epidihydrodideoxystreptose

2-Hydrogen Phthaloyl Derivative of dl-4-Epidihydrodideoxystreptose. dl-4-Epidihydrodideoxystreptose (1.2 g., 9.25 mmole) and 1.345 g. (9.1 mmole) of freshly recrystallized phthalic anhydride were dissolved in 10 ml. of dry pyridine. The solution was heated on a steam bath for 20 hr., cooled, and then poured into 70 ml. of water. Sodium bicarbonate was added until the solution was saturated; the resulting solution was extracted with chloroform until the odor of pyridine had disappeared. The pH of the aqueous solution was then adjusted to 1.0 with 5% hydrochloric acid and the solution was extracted with four 100-ml. portions of chloroform. The combined chloroform extract was dried, and the solvent was evaporated. This yielded 2.068 g. (81.2%, assuming the material consisted of only the 2-hydrogen phthaloyl derivative of dl-4-epidihydrodideoxystreptose) of a tan glass that resisted crystallization from a variety of solvents.

The glass (2.068 g.) from above was chromatographed over silicic acid (50 g.) using 2% methanol in chloroform. Fraction 1 (400 ml.) contained 179 mg. of gum that resisted crystallization and was not investigated further. Fraction 2 (300 ml.) contained 1.608 g. of a colorless glass that resisted crystallization from a variety of solvents. Fraction 3 (200 ml.) contained 329 mg. of glass that resisted crystallization. Fraction 2 was dissolved in benzene-isopropyl ether (1:1); after the solution had been refrigerated for 5 months, crystalline material was obtained. This crystalline material (ca. 1.4 g.) was recrystallized five times from benzene for analysis and furnished 747 mg. of material that showed m.p. 109-111°.

Anal.	$C_{14}H_{16}O_6$	Calc'd: C, 60.00; H, 5.75
	(280.3)	Found : C, 60.32; H, 6.03

The n.m.r. spectrum (20%, deuteriochloroform) of the material showed absorptions at 2.07-2.75 (6H, complex), 4.78 (1H, doublet, J = 5.4; each component split into a doublet, J = 3.0), 5.79 (1H, doublet, J = -11.1; each component split into a doublet, J = 5.4), 6.09 (1H, doublet, J = -11.1; each component split into a doublet, J = 3.0), 6.10 (1H, quartet, J = 6.4), 8.71 (3H, singlet), and 8.82 τ (3H, doublet, J = 6.4).

The infrared spectrum (KBr pellet) showed λ_{max} 2.87, 3.35, 5.84, 6.16, 7.37, 7.97, 8.21, 9.15, and 12.49 μ, among others.

TLC analysis of the unchromatographed material using silica gel HF_{254} as the adsorbant and benzene-methanol-acetic acid (50:4:2) as the solvent system showed spots at R_F 0.21 (weak, phthalic anhydride), 4.0 (strong), 0.49 (strong), and 0.69 (medium). Two developments were used, and visualization was accomplished using long wavelength (366 mμ) U.V.

light.

A portion (771 mg.) of the unchromatographed reaction product from a preparation similar to the one described above was dissolved in 20 ml. of chloroform-acetic acid (95:5) and was boiled under reflux for four days. At the end of this time the solvent was evaporated, and 672 mg. of a brown glass was obtained. TLC analysis of this material under the same conditions as above showed spots at R_F 0.21 (weak, phthalic anhydride), 0.40 (moderate), and 0.49 (strong).

Attempted Preparation of 2-l-Menthoxyacetyl Derivatives of dl-4-Epidihydrodideoxystreptose. To a solution of 1.118 g. (8.45 mmole) of dl-4-epidihydrodideoxystreptose in 30 ml. of dry benzene, 700 mg. (9.0 mmole) of dry pyridine was added. The mixture was cooled in an ice bath and, while stirring, a solution of 0.973 g. (8.46 mmole) of freshly distilled l-menthoxyacetyl chloride in 20 ml. of dry benzene was added dropwise. When the addition was complete, the mixture was allowed to stand overnight and was then washed with three 50-ml. portions of 2% hydrochloric acid and with two 50-ml. portions of water. The benzene solution was dried, and the solvent was evaporated. This yielded 2.486 g. (90.2%) of the sirupy 2-l-menthoxyacetyl derivatives of dl-4-epidihydrodideoxystreptose. This material resisted crystallization from a variety of solvents.

The infrared spectrum (film) showed λ_{max} 2.80, 3.35, 5.66, and 6.90 μ, among others.

Chromatography of the material over silicic acid using chloroform furnished no fractions that could be obtained crystalline after numerous attempts at crystallization from a variety of solvents.

Attempted Preparation of the d-Bornyloxyacetyl Derivatives of dl-4-Epidihydrodideoxystreptose. dl-4-Epidihydrodideoxystreptose (519 mg., 3.93 mmole) was dissolved in 25 ml. of dry benzene that contained 330 mg. (4.23 mmole) of dry pyridine. A solution of 906 mg. (4.22 mmole) of d-bornyloxyacetyl chloride in 10 ml. of dry benzene was then added dropwise while stirring and cooling. When the addition was complete, the mixture was allowed to stand overnight. A 50-ml. portion of benzene was then added, and the resulting mixture was washed with three 25-ml. portions of water. The benzene solution was dried, and the solvent was evaporated. This yielded 1.161 g. (90.7%) of the sirupy 2-d-bornyloxyacetyl derivatives of dl-4-epidihydrodideoxystreptose. This material resisted crystallization from a variety of solvents.

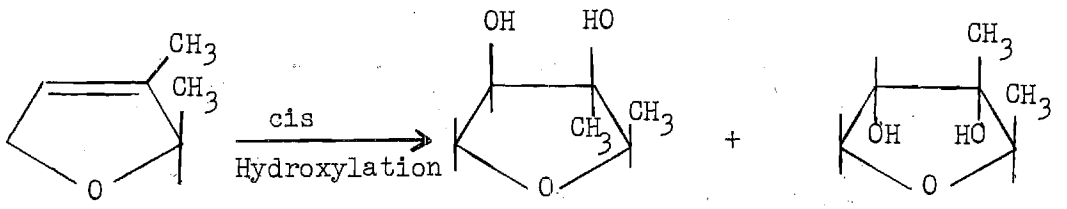
The infrared spectrum (film) of the preparation showed λ_{max} 2.80, 3.32, 5.68, 6.88, 8.32, 8.84, 9.80, and 11.41 μ, among others.

CHAPTER III

DISCUSSION OF RESULTS

The purpose of this research was to accomplish a definitive synthesis of 3-C-methyl-1,5-dideoxy-L-lyxofuranose (XIII), the structural formula assigned to L-dihydrodideoxystreptose, and to show that the synthetic material was identical with a sample of this substance derived from streptomycin. This synthesis would complete the unequivocal synthetic structural proof of the three component parts of the streptomycin molecule, and would thereby make a planned synthesis of streptomycin possible.

The final step in the proposed synthetic route to L-dihydrodideoxystreptose (XIII) was the cis-hydroxylation of 2,3-dimethyl-2,5-dihydrofuran (XVIII). This reaction was expected to produce a mixture of dl-dihydrodideoxystreptose (XIX) and dl-4-epidihydrodideoxystreptose (XX). It was expected that one of the products would predominate, and that this would depend on the method of hydroxylation used.



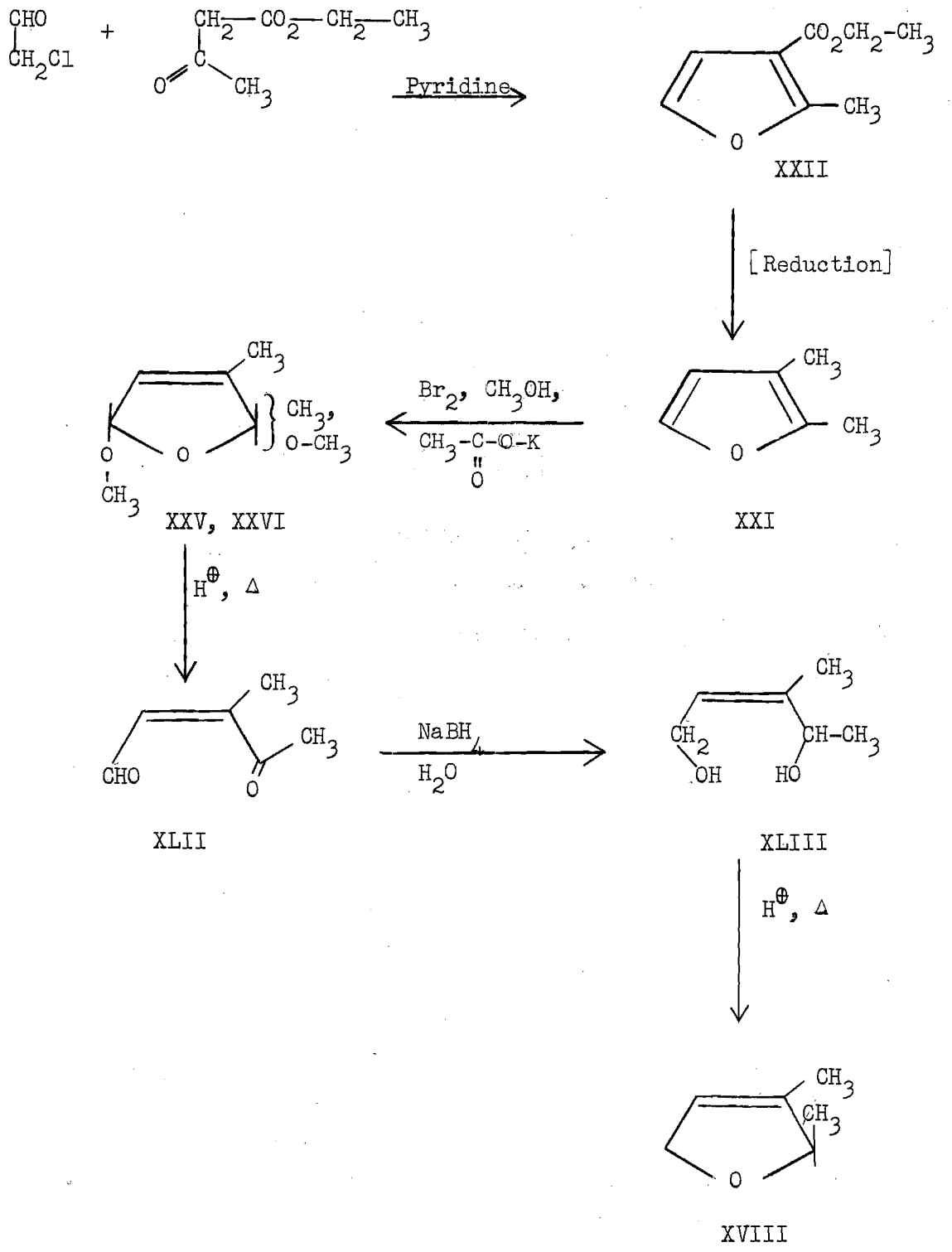
XVIII XIX XX

The proposed synthetic pathway to 2,3-dimethyl-2,5-dihydrofuran started from 2,3-dimethylfuran (XXI). Two syntheses of 2,3-dimethylfuran have been previously recorded in the literature, and both are multistep sequences that give poor overall yields. Reichstien and Grussner (59) prepared 2,3-dimethylfuran in a seven-step synthesis that resulted in a 1.5% overall yield. A more recent synthesis (46) of the compound by a seven-step sequence that started from 2-furoic acid has been accomplished and gave an overall yield of 17.7%. Because of the obvious importance of obtaining maximum yields of intermediates in a multistep synthesis, a synthesis of 2,3-dimethylfuran superior to either of those reported in the literature was desired.

The condensation of chloroacetaldehyde and ethyl acetoacetate in the presence of pyridine is known (45) to furnish ethyl 2-methylfuran-3-carboxylate (XXII) in good yield. It was hoped that some method of reduction could be found that would convert ethyl 2-methylfuran-3-carboxylate into 2,3-dimethylfuran in good yield, and that the 2,3-dimethylfuran could then be converted by the sequence of reactions shown below to 2,3-dimethyl-2,5-dihydrofuran.

Ethyl 2-methylfuran-3-carboxylate (XXII) was prepared by a modification of the method of Winberg _et al._ (45), who obtained the compound contaminated with ethyl acetoacetate in a yield of 63%. It was found when the modified work-up procedure previously described (60) was used, a 67.5% yield of pure material could be obtained.

The absorptions in the n.m.r. spectrum of ethyl 2-methylfuran-3-carboxylate were assigned as shown below.


CHO
CH2Cl
+
CH2—CO2—CH2—CH3
O
C
CH3
Pyridine
CO2CH2-CH3
CH3
O
XXII
[Reduction]
CH3
CH3
O
XXI
Br2, CH3OH,
CH3-C-O-K
O
CH3
CH3,
O-CH3
O
O
CH3
XXV, XXVI
H⊕, Δ
CH3
CH3
CHO
O
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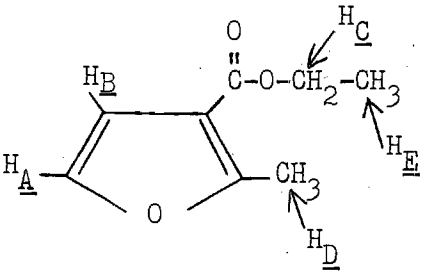
HO
XLIII
H⊕, Δ
CH3
CH3
O
XVIII



XXIII

H	τ	J, cps
A	2.62	AB = 2.1
B	3.28	AD = 0.4
C	5.68	BD = 0.4
D	7.43	CE = 7.0
E	8.69	

The reaction of α,β-dichloroethyl ether with ethyl acetoacetate in 10% sodium hydroxide is also known (61) to produce ethyl 2-methylfuran-3-carboxylate. This synthesis was performed and gave only a 41.5% yield of the desired product; the method was not utilized further.

Since ethyl benzoate can be catalytically reduced to toluene and ethanol in almost quantitative yield (62), the first method considered for the conversion of ethyl 2-methylfuran-3-carboxylate to 2,3-dimethylfuran was the direct catalytic hydrogenolysis of the carbethoxy group to a methyl group. As a model for this reaction ethyl 2-furoate was chosen. Attempted hydrogenolysis of ethyl 2-furoate using either 10% palladium on carbon or 5% palladium on barium sulfate at atmospheric pressure and room temperature resulted in the absorption of two molar equivalents of hydrogen and the formation of the corresponding tetrahydrofuran derivative. The strong carbonyl absorption at 5.73 μ in the infrared spectrum of the product of both reductions was taken as evidence for the reduction of the furan nucleus; the starting ethyl 2-furoate showed λ_{max} for the carbonyl group at 5.89 μ.

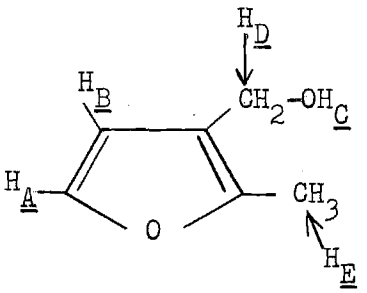
Because catalytic reductive transformation of the carbethoxy group to a methyl group did not proceed under accessible reaction conditions,

this method of reduction was abandoned.

The possibility of the reduction of ethyl 2-methylfuran-3-carboxylate to 2,3-dimethylfuran through 2-methyl-3-hydroxymethylfuran (XXIII) was next considered, because several general methods are available for the conversion of alcohols to the corresponding hydrocarbons.

Reduction of ethyl 2-methylfuran-3-carboxylate with lithium aluminium hydride to 2-methyl-3-hydroxymethylfuran was performed by a modification of the published (45) procedure. It was found that when the molar ratio of lithium aluminium hydride to the ester was increased from 0.650 to 0.762, and when the reaction time was increased from 2.5 hr. to 12 hr., the reported yield of 83% could be increased to 93%.

All absorptions in the n.m.r. spectrum of 2-methyl-3-hydroxylmethylfuran were assigned and are shown below.



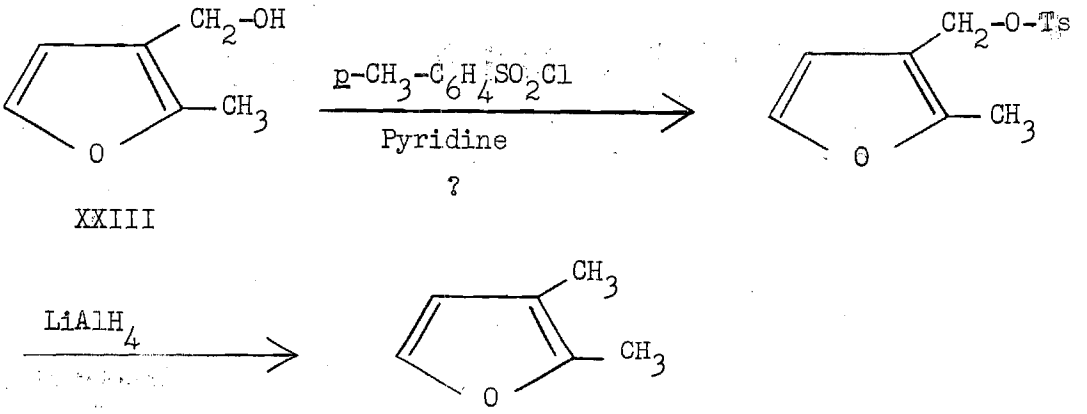
XXIII

H	τ	J, cps
A	2.71	AB = 1.9
B	3.59	
C	5.21	
D	5.63	
E	7.83	

Since reduction of primary p-toluenesulfonate esters with lithium aluminium hydride is known (63) to result in the replacement of the p-tosyloxy group by hydrogen, it was hoped that the p-toluenesulfonate ester could be prepared and subjected to reduction with lithium aluminium

hydride, which would yield 2,3-dimethylfuran.

Since furfuryl alcohol is commercially available, it seemed advisable to use this compound as a model to determine optimum reaction condi-



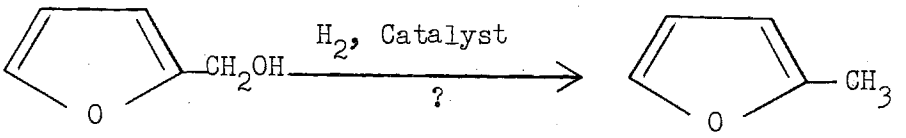
XXIII

XXI

tions for the preparation of the p-toluenesulfonate ester and the reduction. The model p-toluenesulfonate of furfuryl alcohol could not be prepared, so the preparation of the p-toluenesulfonate of 2-methyl-3-hydroxymethylfuran was not attempted. It has been previously reported (64) that the p-toluenesulfonate ester of furfuryl alcohol is unstable and cannot be isolated. This conclusion was verified using the mildest possible reaction conditions. After removal of solvent from the crude product, the material began to decompose almost immediately; a dark green color developed, and within several hours the material had changed to a viscous black tar.

Since alcohols of the benzyl type are known (65) to undergo hydrogenolysis and to yield the corresponding hydrocarbon, the hydrogenolysis of 2-furfuryl alcohol, which would give 2-methylfuran, was attempted as

a model reaction for the hydrogenolysis of 2-methyl-3-hydroxymethylfuran. Reduction of 2-furfuryl alcohol, using five per cent palladium on carbon at room temperature and atmospheric pressure resulted in the absorption of two molar equivalents of hydrogen and the formation of 2-tetrahydro-



XXVII

furfuryl alcohol. The infrared spectrum of the product was identical with that of an authentic sample. This method of conversion of 2-methyl-3-hydroxymethylfuran into 2,3-dimethylfuran was then abandoned.

Reduction of ethyl 5-chloromethylfuran-2-carboxylate to ethyl 5-methylfuran-2-carboxylate using zinc and acetic acid has been reported (66) to proceed in 80% yield. In view of this fact, reduction of 2-methyl-3-chloromethylfuran with zinc and acetic acid was attempted. Employing the published procedure, 2-methyl-3-hydroxymethylfuran was converted into 2-methyl-3-chloromethylfuran (XXIV), using thionyl chloride and pyridine in ether solution. As reported (45), the compound was observed to be unstable; it was necessary to prepare the compound and use it immediately in the synthesis of 2,3-dimethylfuran.

Attempted reduction of 2-methyl-3-chloromethylfuran using zinc and acetic acid failed to produce 2,3-dimethylfuran. Immediately after the addition of the 2-methyl-3-chloromethylfuran to the acetic acid, the solution turned black and in several minutes lumps of carbonaceous material

were observed in the reaction mixture. Presumably the failure of the 2-methyl-3-chloromethylfuran to be stable in the reaction mixture prior to reduction is because of the lack of an electron withdrawing group, as is present in ethyl 5-chloromethylfuran-2-carboxylate.

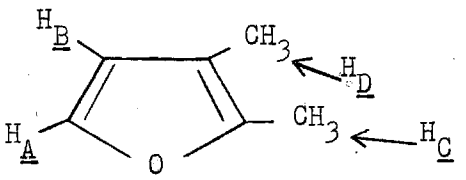
A widely known method for conversion of organic halides to the parent hydrocarbon is the conversion of the halide to the corresponding Grignard reagent and subsequent hydrolysis. This method of reduction of 2-methyl-3-chloromethylfuran to 2,3-dimethylfuran was next attempted. The reaction was difficult to get started, presumably because of the difficulty of obtaining the unstable 2-methyl-3-chloromethylfuran in a high state of purity. Once started, however, most of the calculated quantity of magnesium reacted, but treatment of the resulting ether solution with water furnished, after work-up, only a small quantity of volatile material that contained no 2,3-dimethylfuran. The high reactivity of benzylic Grignard reagents and their tendency to couple with the starting halide is well known (89). Presumably, the failure of this reaction sequence to produce 2,3-dimethylfuran is because of the high reactivity of both the Grignard reagent and the starting 2-methyl-3-chloromethylfuran.

Reduction of allylic and benzylic (67) halides to the corresponding hydrocarbons using lithium aluminium hydride has been shown to give good to excellent yields. This method of reduction of 2-methyl-3-chloromethylfuran to 2,3-dimethylfuran was utilized, and was found to produce the desired product in 57% yield, based on the starting 2-methyl-3-hydroxymethylfuran. Because of the large amount of 2,3-dimethylfuran required as a starting material for the synthesis of dl-dihydrodideoxystreptose, the conversion of 2-methyl-3-hydroxymethylfuran to 2,3-dimethylfuran was

carried out a number of times. It was found that a maximum yield of 2,3-dimethylfuran was obtained if the intermediate 2-methyl-3-chloromethylfuran was not isolated but was handled in ether solution and the crude compound reduced directly.

It was also found that the yield of 2,3-dimethylfuran was lowered if the molar ratio of lithium aluminium hydride to 2-methyl-3-hydroxymethylfuran was less than 0.87:1. Increasing the molar ratio did not improve the yield. In order to obtain a good yield of 2,3-dimethylfuran from 2-methyl-3-hydroxymethylfuran, it was essential that the reaction mixture containing 2-methyl-3-chloromethylfuran be worked up without delay and the reduction performed as soon as drying of the ether solution was complete. The overall yield of 2,3-dimethylfuran based on chloroacetaldehyde for four steps, one of which does not require purification of the intermediate, was 36%.

The observed physical constants for 2,3-dimethylfuran were in agreement with those reported in the literature (46,59) and the n.m.r. spectrum of the compound, which is described below, was quite definitive. Both



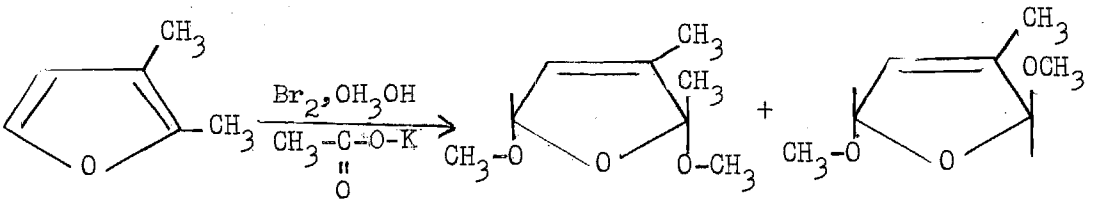
XXI

H	τ	J, cps
A	2.91	AB = 1.95
B	3.94	
C	7.93	
D	8.16	

methyl groups of the compound were closely spaced multiplets consisting

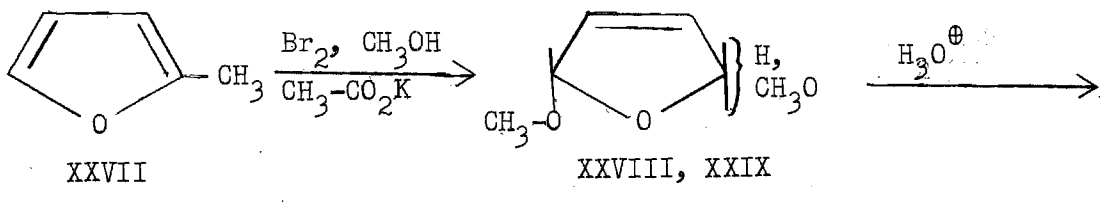
of at least nine major lines each. The protons attached to the furan nucleus appeared as doublets, each member of which was split into at least five lines. Every proton in the molecule is therefore coupled to every other proton in the molecule.

The next step in the proposed synthesis was the oxidation of 2,3-dimethylfuran to a mixture of the cis- (XXV) and trans- (XXVI)-2,5-dimethoxy-2,3-dimethylfurans using bromine in methanol.

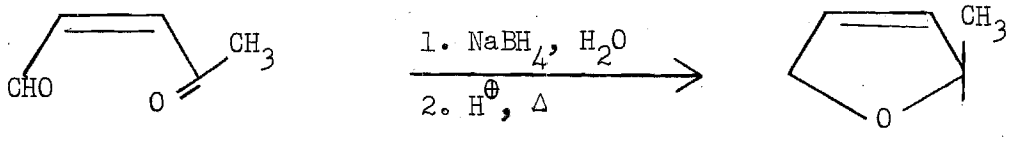


XXI XXV XXVI

Since 2-methylfuran (XXVII) was readily available, it seemed desirable to carry the proposed reaction sequence through using this compound, and compounds derived from it, as models for the corresponding compounds of the 2,3-dimethylfuran series. This reaction sequence is shown below.



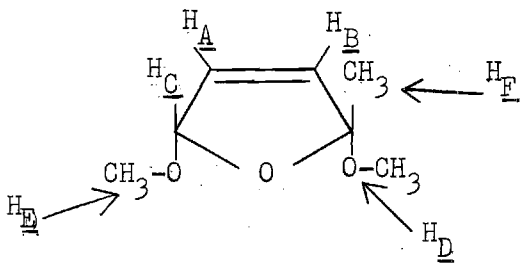
XXVII XXVIII, XXIX



XXXI XLV

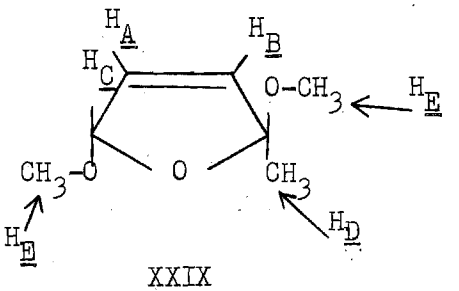
The oxidation of 2-methylfuran was performed using a modification of the procedure described in the literature (35). By keeping the temperature of the reaction mixture below -30°, instead of at -7° as described, it was found that the methanolic solution of bromine could be added in about one-half the time required in the published procedure and that the yield was increased from 65% to 70%.

The observed physical constants for the preparation were in agreement with those reported in the literature and the n.m.r. and infrared spectra were consistent for a mixture of the cis and trans isomers. The n.m.r. spectrum of the preparation, which is described below, indicated that the ratio of the cis-isomer (XXVIII) to the trans-isomer (XXIX) was approximately 2:1.



XXVIII

H	τ
A,B	3.82-4.16
C	4.52
D	6.59
E	6.91
F	8.60



XXIX

H	τ
A,B	3.82-4.16
C	4.24
D	6.66
E	6.95
F	8.53

The absorptions of H_A, H_B, and H_C in both the cis- and trans-isomers

appeared as multiplets that were too complicated to be analyzed.

The assignment of the major component in the product as the cis isomer and the minor component as the trans isomer was made by consideration of the n.m.r. spectrum of the preparation. The absorptions resulting from the two O-methyl groups of the major component of the preparation occur at lower field than the absorptions resulting from the two O-methyl groups of the minor component and the former are therefore deshielded to a greater extent. This would be expected if the two O-methyl groups were on the same side of the ring since mutual deshielding resulting from the anisotropic effect of the carbon-oxygen bond would occur. This type of deshielding could not occur if the O-methyl groups were trans . The minor component of the preparation must therefore have the trans arrangement of the O-methyl groups. The fact that the absorption resulting from the C-methyl group of the minor component occurs at lower field than the C-methyl group of the major component, and the former is therefore less shielded, supports this conclusion. In the component with the cis arrangement of the methoxyl groups, no deshielding of the C-methyl group by interaction with the O-methyl group at C_5 can occur since the two groups are on opposite sides of the ring. The C-methyl group of the cis component and therefore absorbs at higher field than the C-methyl group of the trans compound. In the trans compound, however, the C-methyl group is on the same side of the ring as the O-methyl group at C_5, and deshielding can occur. The C-methyl group of the cis compound would be expected to absorb at higher field and is therefore consistent with its formulation as the major component. The higher absorption of H_C in the major component resulting from the oxidation of 2-methylfuran than in the minor component further supports

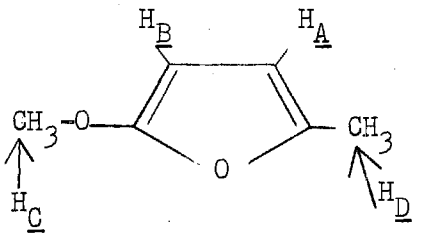
the previous assignments. In the minor component it is deshielded by the O-methyl group at C_2 since it is on the same side of the ring. In the major component H_C is on the same side of the ring as the C-methyl group and would be expected to absorb at higher field, as observed.

The above discussion is based in part on the observation (98) that an axial hydrogen is deshielded by 0.39-0.50 ppm by an axial (1,3) hydroxyl group in rigid 6-membered ring systems of steroids.

Although no previous effort has been made to assign the relative orientation of the methoxy groups in the higher and lower boiling 2,5-dimethoxy-2-methyl-2,5-dihydrofurans, the geometrical configurations of the higher and lower boiling 2,5-dimethoxy-2,5-dihydrofurans have been determined (68). The higher and lower boiling isomers were separated by distillation using a spinning band column. The higher boiling isomer formed four adducts with cyclopentadiene and was therefore the cis isomer. The lower boiling isomer formed only two adducts with cyclopentadiene and was therefore the trans isomer. It has been shown by consideration of the n.m.r. spectrum of the preparation that the cis isomer is the predominant product (55:45) when furan is oxidized with bromine and methanol at -7° (99).

Partial separation of the cis (XXVIII) and trans (XXIX) isomers of 2,5-dimethoxy-2-methyl-2,5-dihydrofuran was accomplished by careful distillation at reduced pressure using a lab-size spinning band column. The distillate was enriched in the higher boiling cis compound to an extent of 85%, as shown by integration of the n.m.r. spectrum. This mixture of isomers has been reported (35) to be distillable at atmospheric pressure without decomposition.

The preparation of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfurans was also carried out using a modified procedure (69) that was experimentally more difficult. This procedure required neutralization of the hydrogen bromide produced with ammonia at -80°. The yield was lower (32%) and the product, after standing two weeks, was found to be contaminated with 2-methyl-5-methoxyfuran (XXX). The 2-methyl-5-methoxyfuran was obtained pure by distillation, using a spinning band column and the physical constants observed for the compound were in agreement with the recorded (70) values. The absorptions in the n.m.r. spectrum are given below. The formation of 2-methyl-5-methoxyfuran presumably resulted



XXX

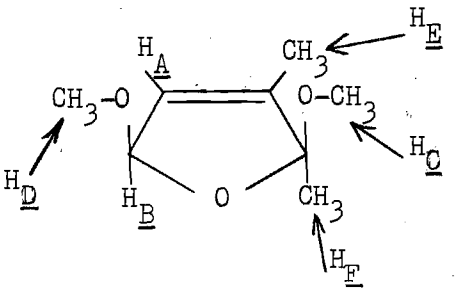
H	τ	J
A	4.25	AB = 3.3
B	5.05	AD = 1.2
C	6.25	BD = 0.3
D	7.92	

from the elimination of methanol catalyzed by traces of hydrogen bromide in the product (70).

The preparation of cis- and trans-2,5-dimethoxy-2,3-dimethyl-2,5-dihydrofuran was performed using the same reaction conditions that had been successfully applied to 2-methylfuran. The yield was better and amounted to 84%.

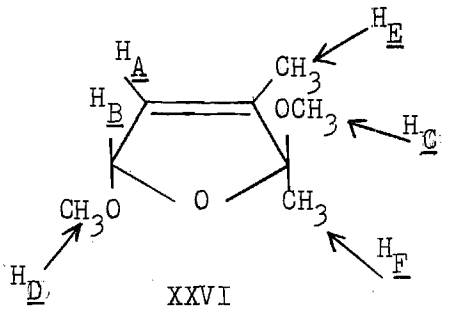
The elemental analysis, infrared spectrum, and n.m.r. spectrum of the preparation were consistent for a cis-trans mixture of 2,5-dimethoxy-2,3-dimethyl-2,5-dihydrofuran. The relative ratio of the cis isomer to

the trans isomer in the purified material of b.p. 61-63°/15 mm. was 2:1, as determined by integration of the n.m.r. spectrum; the assignments are given below. The absorptions of H_A and H_B appeared as multiplets in both



XXV

H	τ
A	4.28-4.48
B	4.63-4.75
C	6.61
D	6.94
E	8.22-8.37
F	8.76



XXVI

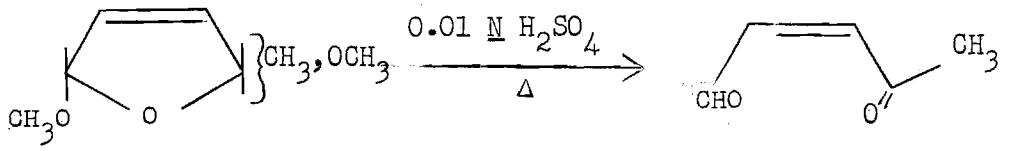
H	τ
A, B	4.28-4.48
C	6.70
D	7.03
E	8.22-8.37
F	8.60

the cis (XXV) and trans (XXVI) compounds and were too complicated to be analyzed. The olefinic methyl group appeared as a multiplet that was also too complicated to be analyzed.

The assignment of the major component as the cis isomer and the minor component as the trans isomer in the purified preparation was made using arguments previously described for the assignment of the major and

minor components in the mixture of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran.

As a model reaction for the next step in the synthesis of dl-dihydrodideoxystreptose, the acid catalyzed hydrolysis of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran to 4-oxo-cis-2-pentenal (XXXI) was attempted as described in the literature (35). Several attempts were made



XXVIII and XXIX XXXI

to isolate 4-oxo-cis-2-pentenal from brief treatment of the mixture of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran with warm 0.01 N sulfuric acid. The material obtained had the same boiling point as that quoted in the literature. There remained after distillation a large quantity of resinous material. The n.m.r. spectrum of the distilled material had little absorption that would result from the aldehyde proton or vinyl protons; hence the product contained no appreciable quantity of 4-oxo-cis-2-pentenal. Efforts to prepare a bis-2,4-dinitrophenylhydrazone of this material were unsuccessful; however, this derivative of 4-oxo-cis-2-pentenal is described (35) and is said to have been prepared from the hydrolysate of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfurans with warm 0.01 N sulfuric acid.

The failure to isolate 4-oxo-cis-2-pentenal under these conditions

probably resulted from heat or acid catalyzed rearrangements during the hydrolysis or distillation.

Although it was clear that the acid catalyzed hydrolysis of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran did not produce 4-oxo-cis-2-pentenal, the nature of the preparation obtained was investigated. The infrared spectrum of the preparation showed the presence of at least three different carbonyl absorptions at 5.73, 5.79, and 5.89 μ. The infrared spectrum of 4-oxo-cis-2-pentenal obtained (90) by a different method of hydrolysis showed only λ_{max} 5.91 μ for the carbonyl absorptions.

The unknown carbonyl compound was reduced with potassium borohydride. This product had a boiling point that was in agreement with that reported in the literature (36) for cis-2-pentene-1,4-diol. The infrared spectrum showed absorption resulting from hydroxyl groups but none due to carbonyl groups. The n.m.r. spectrum was complicated and could not be analyzed completely. That the preparation was a mixture was indicated by the appearance of two doublets at 8.82 and 8.85 τ.

In an attempt to cyclize any 1,4-diol present in the above preparation, the material was heated with Dowex 50W-X8 ion-exchange resin. The liquid product that was obtained in fair yield had a boiling range of 130-136°. That the preparation obtained was a mixture was indicated by the appearance of two doublets at 8.80 and 8.85 τ in the n.m.r. spectrum. The infrared spectrum showed the absence of a hydroxyl group and the presence of only a very weak absorption resulting from a carbonyl group. A small amount of 2,4-dinitrophenylhydrazone could be obtained from the preparation. Analytical results that were obtained for the liquid substance were in reasonably good agreement for the formula $C_6H_{12}O_2$.

The mixture could not be resolved by preparative GLC. In an attempt to resolve the mixture into its components the substance was distilled, using a lab-size spinning band column and a reflux ratio of approximately 100:1. Eleven fractions of approximately equal quantity were taken. The n.m.r. spectra of fractions two and ten were virtually superimposable; the major difference was in the appearance of the methyl group doublets; the difference amounted only to a ten per cent change in composition. Fraction three gave an immediate precipitate with 2,4-dinitrophenylhydrazine reagent, fraction six gave only a small amount of precipitate, and fraction eleven did not give a precipitate when allowed to stand at room temperature for two days. From the weight of 2,4-dinitrophenylhydrazone obtained, fraction three contained only about five per cent of carbonyl compounds.

Using the data available, a definitive structure for this compound cannot be derived. The absorptions present in the n.m.r. spectrum, however, do lead to some suggestions and exclusions. The two doublets at 8.80 and 8.85 τ (3 protons) obviously result from methyl groups in the situation ($CH_3-C(=O)-H$). The strong singlets at 6.75 and 6.80 τ (three protons) obviously result from the protons of methoxyl groups. The complicated absorptions from 5.8-6.6 τ are caused by four protons; these must be attached to carbon that is also attached to oxygen. The absorptions centered at 7.9 and 8.5 τ, each corresponding to one proton, are protons bonded to carbon that is only bonded to carbon or hydrogen.

The data available suggest that the substance obtained is a mixture of <u>cis</u>- and <u>trans</u>-methylmethoxytetrahydrofurans. That the methoxyl group might be situated in an α position is excluded by (1) the stability of the preparation to acid and (2) the absence of a proton at less than

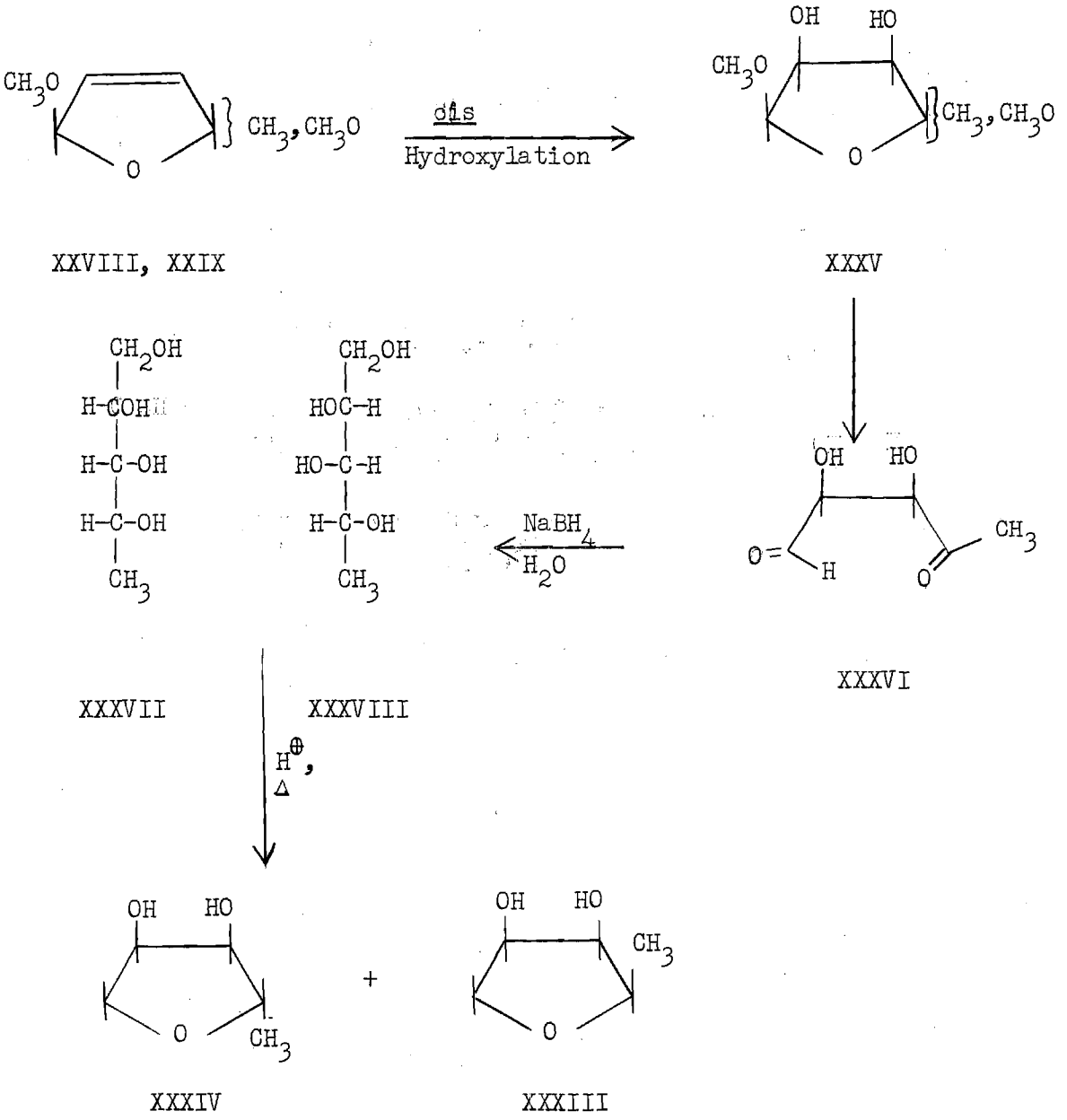
5.8 τ in the n.m.r. spectrum. The only tetrahydrofuran derivatives remaining as possibilities are 2-methyl-3-methoxytetrahydrofuran and 2-methyl-4-methoxytetrahydrofuran. A decision as to the structural formula of the compounds obtained, or a rational mechanism for their formation, cannot at this time be made.

Since acid catalyzed cyclization of meso-erythritol has been shown (33) to furnish meso-3,4-dihydroxytetrahydrofuran (XXXII) in 94% yield, a modification of the original route to dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV) was attempted. The modified portion of the route is summarized below.

cis-Hydroxylation of the mixture of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran (XXVIII, XXXIX) would be expected to furnish a mixture of diastereoisomeric 3,4-dihydroxy-2,5-dimethoxy-2-methyltetrahydrofurans (XXXV). This mixture of cyclic acetals would then be subjected to mild acid hydrolysis to give the 2,3-dihydroxy-4-oxopentanal XXXVI. Reduction of XXXVI, using sodium borohydride would then be expected to furnish a mixture of dl-5-deoxyribitol (XXXVII) and dl-5-deoxylyxitol (XXXVIII).

It was anticipated that cyclization of the mixture of dl-5-deoxyribitol (XXXVII) and dl-5-deoxylyxitol (XXXVIII) in a manner analogous to that used for the cyclization of meso-erythritol, would furnish a mixture of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV).

cis-Hydroxylation of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfurans (XXVIII, XXVIX) was first attempted using the silver acetate-iodine-wet acetic acid reagent (71). Only an intractable tar could be



isolated from this reaction mixture. The failure of the reaction presumably results from rearrangements and/or side reactions catalyzed by the acetic acid or the heat used in the reaction.

Hydroxylation of olefins using osmium tetroxide and a solution of hydrogen peroxide in t-butyl alcohol is well known (72) to result in the cis orientation of the hydroxyl groups. This method of hydroxylation of

cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran (XXVIII, XXVIX) using the method of Milas and Sussman (72) was next attempted. Isolation of the intermediate mixture of 3,4-dihydroxy-2,5-dimethoxy-2-methyltetrahydrofurans (XXXV) or the 2,3-dihydroxy-4-oxopentanal (XXXVI) that resulted from the treatment of XXXV with 0.01 N sulfuric acid was not attempted.

The sirup that resulted from the sodium borohydride reduction of the intermediate 2,3-dihydroxy-4-oxopentanal (XXXVI) resisted crystallization. Since the n.m.r. spectrum of this preparation was much more complicated than would be expected for a mixture of dl-5-deoxyribitol (XXXVII) and dl-5-deoxylyxitol (XXXVIII), it was concluded that the preparation was impure.

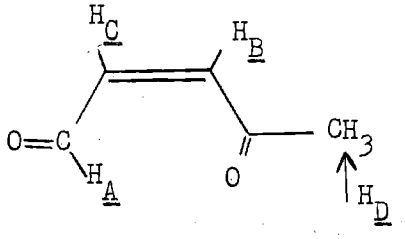
Treatment of the sirup with benzoyl chloride in pyridine furnished, after chromatography over silicic acid, a 3.2% yield of crystalline material that was presumably either the tetrabenzoate of dl-5-deoxyribitol (XXXVII) or dl-5-deoxylyxitol (XXXVIII). Analytical data obtained for this derivative was in fair agreement for either of these diasterisomeric tetrabenzoates.

Acid catalyzed cyclization of the sirup that resulted from the sodium borohydride reduction of the intermediate 2,3-dihydroxy-4-oxopentanal (XXXVI) using the literature procedure (33) for the cyclization of meso-erythritol furnished a 44% yield [assuming the product is a mixture of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV)] of redistilled material that showed b.p. 80-83.0/0.8 mm. The n.m.r. spectrum of this material was not consistent for a mixture of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV) because of the strong absorption at 3.90-4.38 τ that

suggested the presence of olefinic protons. This method of preparation of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV) was then abandoned.

Renewed attempts were then made to find conditions for the hydrolysis of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran that would produce 4-oxo-cis-2-pentenal (XXXI). Hydrolysis of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran (XXVIII, XXIX) to 4-oxo-cis-2-pentenal (XXXI) was achieved by dissolving the dihydrofuran in five times its weight of distilled water and allowing the solution to stand for about sixteen hours at room temperature. Continuous extraction of the resultant solution with ether, evaporation of the ether, and distillation at reduced pressure furnished, in addition to about a 10% yield of recovered starting material, a 46.6% yield of 4-oxo-cis-2-pentenal (XXXI). The compound was unstable as shown by the large quantity of resinous material left after distillation and the fact that resinification of the distilled material took place after standing about a week at room temperature.

The boiling point observed for this compound was in agreement with that recorded (34) in the literature. The infrared and n.m.r. spectra of the distilled material were consistent for 4-oxo-cis-2-pentenal (XXXI). All the absorptions in the n.m.r. spectrum were assigned and are shown below.

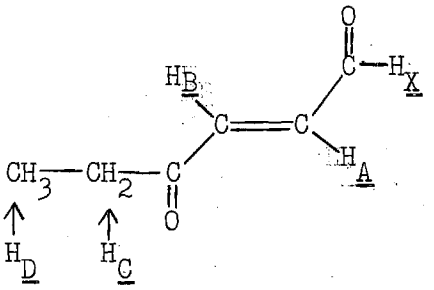


XXXI

H	τ	J, cps
A	0.08	AC = 16.8
B	2.86	BC = 11.8
C	3.84	
D	7.62	

The magnitude of the coupling constant (J_{BC}) is consistent with the assigned cis configuration of the olefinic bond since coupling constants for cis-olefinic protons are known (73) to be 7-12 cps and coupling constants for trans-olefinic protons are known to be 13-18 cps.

Gilby and Waterhouse (74) have isolated 4-oxo-trans-2-hexenal (XXXIX) from the scent glands of the green vegetable bug, Nezara veridula (L.), using preparative GLC, and they have determined the n.m.r. spectrum of this compound. The multiplicities of the aldehydic and olefinic protons could not be explained by first order analysis because of virtual (75) coupling of the aldehydic proton with the olefinic protons. The aldehydic proton appeared as a four-line multiplet. The line positions and intensities observed in the experimental spectrum for the aldehydic and olefinic protons were, however, matched by a computed spectrum using the parameters shown below. The magnitude of the coupling constant (J_{AB}) between the olefinic protons unequivocably proves the trans arrangement of the double bond in this compound.



XXXIX

H	τ	J, cps
A	3.11	AB = 16.62
B	3.22	AX = 7.14
X	0.15	BX = 0.04
C	7.26	CD = 7.30
D	8.83	

The assignment of the cis configuration of the double bond in the 4-oxo-2-pentenal obtained in the previously described hydrolysis is further

supported by the magnitude of the coupling constant (J_{AB}) of the olefinic protons in 4-oxo-trans-2-hexenal and by the fact that no virtual coupling was observed in 4-oxo-cis-2-pentenal (XXXI), since the entire spectrum could be easily explained by first-order analysis.

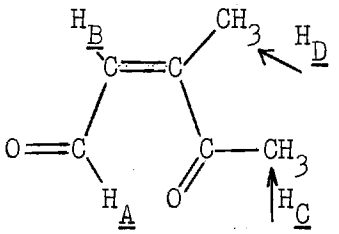
The mixture of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran (XXVIII, XXIX) was converted into a mixture of cis-2-pentene-1,4-diol (XL) and 1,4-pentanediol (XLI) by hydrolysis to 4-oxo-cis-2-pentenal (XXXI) and reduction of the XXXI with sodium borohydride. It was found that a better overall yield of the mixture of diols from cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran (XXVIII, XXIX) was obtained if the intermediate 4-oxo-cis-2-pentenal (XXXI) was not isolated but was directly reduced in the aqueous hydrolysate. The yield was also improved by heating the aqueous hydrolysate on a steam bath for two hours after hydrolysis at room temperature and before reduction. The small increase in yield observed probably resulted from hydrolysis of starting material that remained unchanged during the hydrolysis at room temperature.

When the reduction of the aqueous hydrolysate was carried out at 0° a 59% overall yield of cis-2-pentene-1,4-diol (XL) and a 10.5% overall yield of 1,4-pentanediol (XLI) was obtained for the two steps. When the reduction was carried out at room temperature the overall yield of cis-2-pentene-1,4-diol was 49.7% and the overall yield of 1,4-pentanediol was 16.3% for the two steps. The composition of the diol mixture in each case was determined by quantitative catalytic hydrogenation.

The hydrolysis of cis- and trans-2,5-dimethoxy-2,3-dimethyl-2,5-dihydrofuran (XXV, XXVI), using distilled water, was accomplished in the manner previously described for cis- and trans-2,5-dimethoxy-2,5-dihydro-

2-methylfuran (XXVIII, XXIX). Distillation of the residue after evaporation of the ether from the extract furnished 58.4% of 3-methyl-4-oxo-cis-2-pentenal (XLII). The boiling point observed for the compound was not in close agreement with the value recorded (47) in the literature for this compound.

The infrared and n.m.r. spectra were consistent for the compound. The n.m.r. spectrum of the compound was quite definitive and all the absorptions were assigned by first-order analysis. The analysis of the n.m.r. spectrum is given below.



XLII

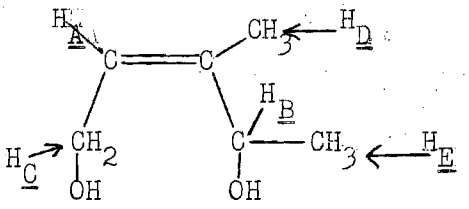
H	τ	J, cps
A	0.34	AB = 7.2
B	3.00	BD = 1.65
C	7.61	
D	7.83	

The conversion of cis- and trans-2,5-dimethoxy-2,5-dihydro-2,3-dimethylfuran (XXV, XXVI) into 3-methyl-cis-2-pentene-1,4-diol (XLIII) was achieved essentially as described for the preparation of cis-2-pentene-1,4-diol (XL) from cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran (XXVIII, XXIX). It was found that the hydrolysis at room temperature required two days for the optimum yield. The sodium borohydride reduction of the aqueous hydrolysate containing 3-methyl-4-oxo-cis-2-pentenal (XLII) was carried out at ice-bath temperature; no evidence for reduction of the carbon-carbon double bond was observed, as was the case for XL, presumably because of deactivation of the double bond by the methyl group.

The yield of 3-methyl-cis-2-pentene-1,4-diol (XLIII) from cis- and trans-2,5-dimethoxy-2,5-dihydro-2,3-dimethylfuran (XXV, XXVI) was 85% for the two steps. Analytical data obtained for the compound were consistent with the expected structure.

An examination of the literature revealed no other general synthetic method for the preparation of cis-2-butene-1,4-diols that have substituents on the double bond. The method described for the preparation of 3-methyl-cis-2-pentene-1,4-diol (XLIII) gave only the cis isomer, and a high (71.5%) overall yield was obtained from 2,3-dimethylfuran (XXI). This method of preparation should be particularly useful for the preparation of substituted cis-2-butene-1,4-diols. The only limitation is the availability of the appropriately substituted furan.

All the absorptions in the n.m.r. spectrum of 3-methyl-cis-2-pentene-1,4-diol (XLIII) were assigned and are shown below.



XLIII

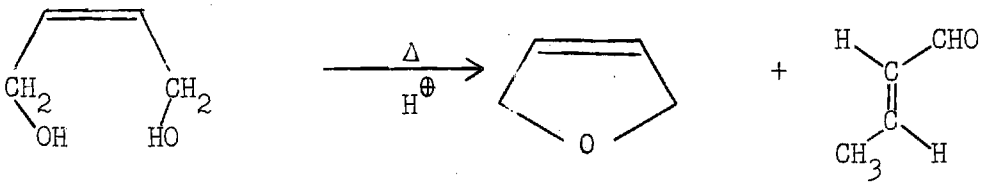
H	τ	J, cps
A	4.59	AC = 7.5
B	5.25	BE = 7.0
C	5.88	
D	8.28	
E	8.79	

The next step in the planned synthesis of dl-dihydrodideoxystreptose (XIX) was the conversion of XLIII to 2,5-dihydro-2,3-dimethylfuran (XVIII).

Since acid catalyzed dehydration of cis-2-butene-1,4-diol (XLIV) is known (31) to produce 2,5-dihydrofuran (XLVI) as the major product, the cyclization of cis-2-pentene-1,4-diol (XL) to 2,5-dihydro-2-methyl-

furan (XLV) was planned as a model reaction for the cyclization of 3-methyl-cis-2-pentene-1,4-diol (XLIII) to 2,5-dihydro-2,3-dimethylfuran (XVIII).

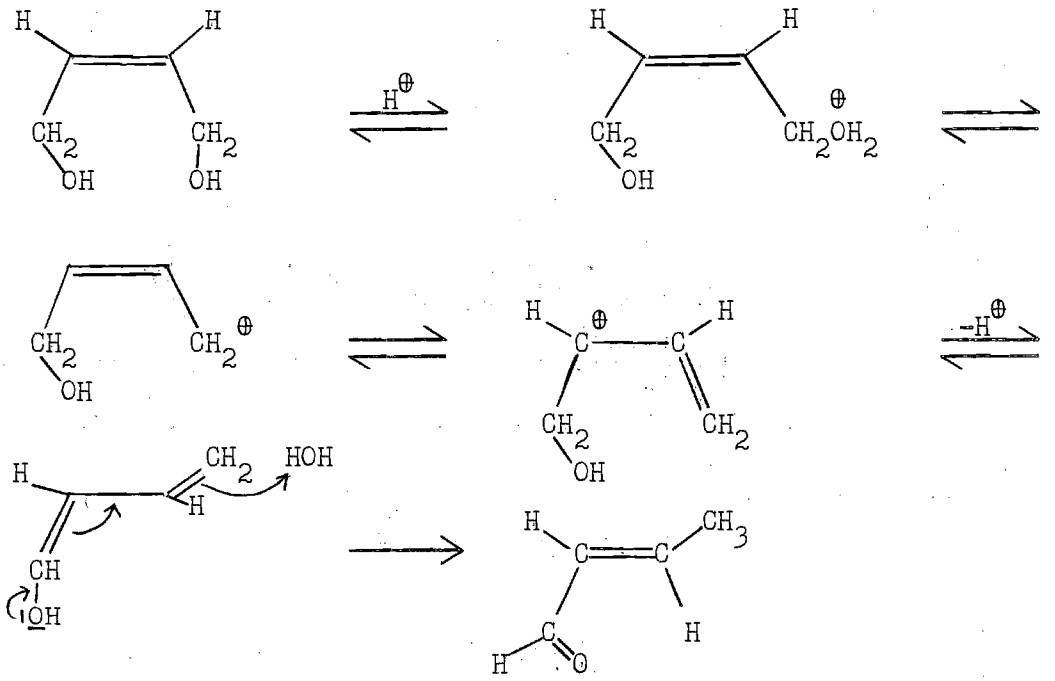
The cyclization of cis-2-butene-1,4-diol (XLIV) was first carried out as a model reaction, using Dowex 50W-X8 ion-exchange resin in the hydrogen phase as the acid catalyst. The reaction was found to give a 59% yield of 2,5-dihydrofuran (XLVI) and a 7.6% yield of trans-crotonaldehyde (XLVII). The separation of XLVI from XLVII was accomplished by distillation using a lab-size spinning band column. The trans-crotonal-



XLIV 59% XLVI 7.6% XLVII

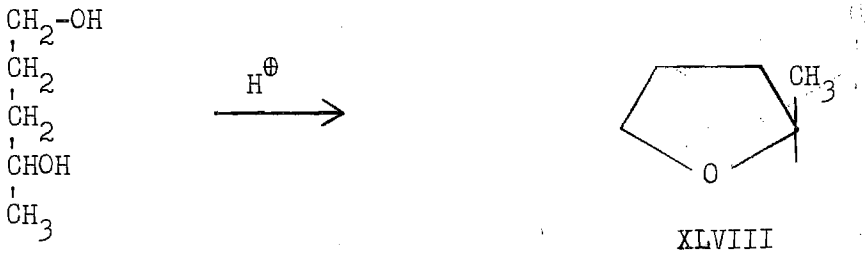
dehyde presumably resulted from an acid catalyzed allylic rearrangement. A possible reaction mechanism for this conversion is shown below.

When a mixture containing 83.5% of 2-pentene-1,4-diol (XL) and 16.5% of 1,4-pentanediol (XLI) was treated with Dowex 50W-X8 ion-exchange resin in a manner identical to that used in the cyclization of cis-2-butene-1,4-diol (XLIV) a 46% yield of 2-methyltetrahydrofuran (XLVIII) (based on the amount of 1,4-pentanediol in the starting material) and an 80.5% yield of trans-2-pentenal (XLIX) was obtained. No 2,5-dihydro-2-methylfuran was detected. The mechanism for the transformation of cis-2-pentene-1,4-diol into trans-2-pentenal is probably analogous to



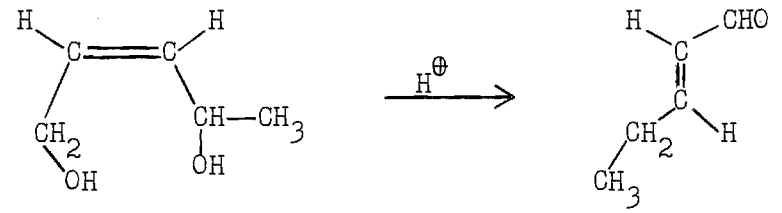
XLVII

that proposed above for the formation of trans-crotonaldehyde from cis-2-butene-1,4-diol.



XLI

XLVIII



XL

XLIX

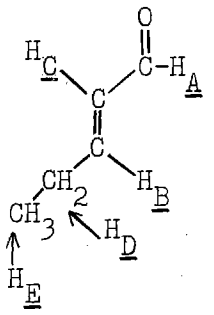
The failure to observe XLV as a reaction product probably results

from the high tendency of cis-2-pentene-1,4-diol (XL) to undergo allylic rearrangement because the hydroxyl group at C_4 is both allylic and secondary, whereas both hydroxyl groups in cis-2-butene-1,4-diol are primary.

The 2-methyltetrahydrofuran (XLVIII) showed a boiling point in agreement with the recorded (38) value and had an n.m.r. spectrum identical with that of an authentic sample.

The trans-2-pentenal (XLIX) showed a boiling point in reasonable agreement with that recorded in the literature (39) and yielded a 2,4-dinitrophenylhydrazone that showed a melting point in agreement with the literature value (39).

The n.m.r. spectrum of trans-2-pentenal (XLIX) was very definitive and was completely analyzable by first-order analysis. This analysis is shown below.

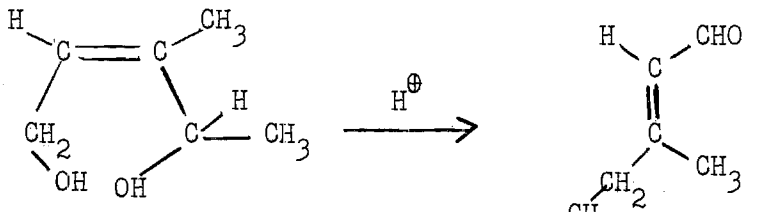


XLIX

H	τ	J, cps
A	0.47	AC = 7.5
B	3.05	BC = 16.0
C	3.91	CD = 1.5
D	7.68	BD = 6.0
E	8.88	DE = 7.5

Attempted acid catalyzed cyclization of 3-methyl-cis-2-pentene-1,4-diol (XLIII) using Dowex 50W-X8 ion-exchange resin under conditions similar to those described for the cyclization of cis-2-butene-1,4-diol (XLIV) gave a 91.4% yield of 3-methyl-trans-2-pentenal (LI). No

2,3-dimethyl-2,5-dihydrofuran (XVIII) could be detected. This compound yielded a 2,4-dinitrophenylhydrazone that showed a melting point in agreement with the value recorded (40) in the literature.

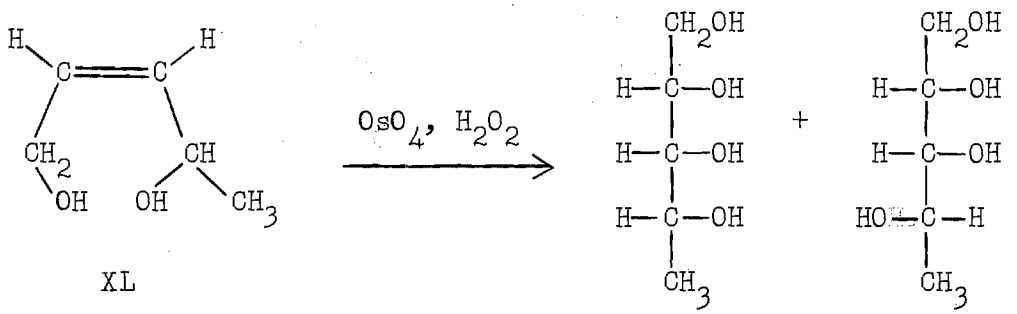


XLIII

LI

Since the attempted acid catalyzed cyclization of cis-2-pentene-1,4-diol (XL) did not yield 2,5-dihydro-2-methylfuran (XLV) because of an allylic rearrangement involving the double bond, it was then decided to perform the cis-hydroxylation of the double bond prior to cyclization, thereby eliminating the possibility of allylic rearrangement. This approach seemed particularly promising since osmium tetroxide-aqueous hydrogen peroxide hydroxylation of cis-2-butene-1,4-diol (XLIV) produces meso-erythritol in 72% yield and acid catalyzed cyclization of meso-erythritol furnishes meso-3,4-dihydroxytetrahydrofuran (XXXII) in 94% yield (76).

The hydroxylation of cis-2-pentene-1,4-diol (XL) was conducted under conditions described for the hydroxylation of cis-2-butene-1,4-diol (XLIV). The XL used in the hydroxylation contained 15.1% of 1,4-pentanediol (XLI). A 66% yield of a sirupy mixture of dl-5-deoxyribitol (XXXVII) and dl-5-deoxylyxitol (XXXVIII) was obtained. The yield was based on the amount of XL present in the starting mixture and it was assumed that all the XLI present was carried through to the product unchanged.

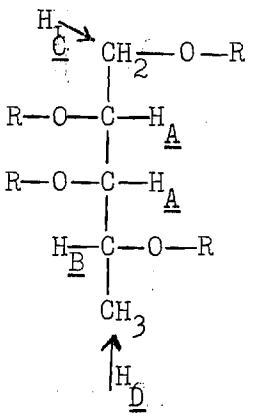


XL XXXVII XXXVIII

Treatment of the mixture of XXXVII, XXXVIII, and XLI with benzoyl chloride in pyridine furnished a 96.5% yield of a sirupy mixture of perbenzoyl derivatives. Crystallization of the mixture from methanol furnished a 39.8% yield of a mixture of tetrabenzoyl dl-5-deoxyribitol (XXXVIIa) and tetrabenzoyl dl-5-deoxylyxitol (XXXVIIIa). In the n.m.r. spectrum of the mixture of XXXVIIa and XXXVIIIa, the methyl groups appeared as two separate doublets and from their relative intensities, a ratio of 5:4 for one of the components to the other was indicated. The analytical data obtained on the preparation was consistent for the expected formula.

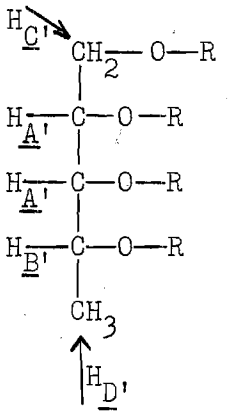
The infrared and n.m.r. spectra of the mixture was consistent for the expected structures. All the absorptions in the n.m.r. spectrum were assigned and are shown below.

One of the two tetrabenzoates of the mixture was obtained pure by chromatography of the mixture over aluminia. Satisfactory analytical data were obtained for the compound, and the n.m.r. spectrum, which is described below, showed only one doublet in the region where the mixture showed two doublets. It was not known which of the two tetrabenzoates was obtained pure.



XXXVIIIa

+

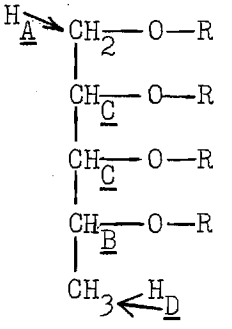


XXXVIIa

H	τ	J, cps
Aromatic	1.75-2.25	BD = 6
	2.30-2.90	B'D' = 6
A, A'	3.84-4.50	
B, B'		
C, C'	4.84-5.88	
D, D'	8.30-8.58	

R = $C_6H_5\overset{O}{\overset{\|}{C}}-$

Acid catalyzed cyclization of the mixture of dl-5-deoxyribitol (XXXVII) and dl-5-deoxylyxitol (XXXVIII) was accomplished using the acid catalyzed conditions described (33) for the cyclization of meso-erythritol. This method of cyclization furnished a 64% yield of a mixture of



R = $C_6H_5\overset{O}{\overset{\|}{C}}-$

XXXVIIa or XXXVIIIa

H	τ	J, cps
Aromatic	1.81-2.29	BD = 6
	2.31-2.88	
A, B	3.91-4.61	
C	4.88-5.67	
D	8.45	

dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV). The reaction product also contained 1,4-pentanediol (XLI). Only approximately 64% of the XLI present in the starting material was observed in the product. Presumably the XLI that was unaccounted

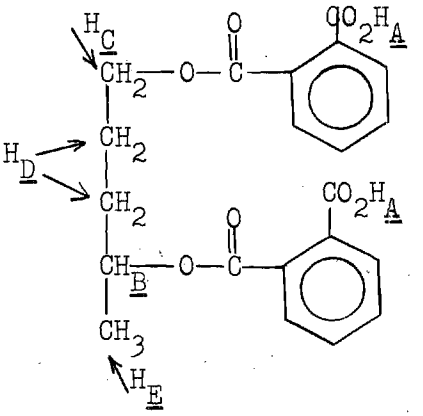
for was cyclized under the reaction conditions to 2-methyltetrahydrofuran (XLVIII). Since the cyclization products were distilled from the reaction mixture under high vacuum all of the volatile XLVIII would not have been observed.

Treatment of the reaction product with benzoyl chloride in pyridine furnished a mixture of the dibenzoates of dl-3-nordihydrodideoxystreptose, dl-3-nor-4-epidihydrodideoxystreptose, and dl-1,4-pentanediol, as shown by the n.m.r. spectrum of the preparation. This mixture resisted crystallization, and chromatography of the mixture over alumina failed to separate the components. The first fractions from the column were enriched in the dibenzoate of XLI and the last fractions from the column were enriched in the dibenzoates of XXXIII and XXXIV.

Treatment of the mixture of XXXIII, XXXIV, and XLI with phthalic anhydride in pyridine yielded, after chromatography of the reaction product over silicic acid, the crystalline bis-hydrogen phthaloyl derivative of XLI (XLIa) and the crystalline bis-hydrogen phthaloyl derivative of XXXIV (XXXIVa). Satisfactory analytical data were obtained for both of the compounds that were obtained crystalline.

The infrared and n.m.r. spectra of XLIa were consistent with the expected structure. All of the absorptions in the n.m.r. spectrum of XLIa were assigned and are shown below.

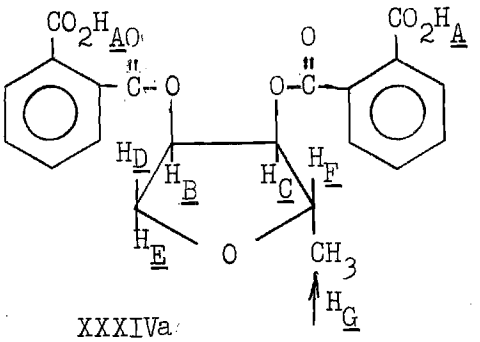
The infrared and n.m.r. spectra of the bis-hydrogen phthaloyl derivative of either XXXIII or XXXIV that were obtained crystalline were consistent for either of the two compounds. All the absorptions in the n.m.r. spectrum of the crystalline bis-hydrogen phthaloyl derivative of XXXIV were assigned and are shown below. That the crystalline



XLIa

H	τ	J, cps
A	-2.34	BE = 6
Aromatic	2.04-2.56	
B	4.56-5.12	
C	5.22-6.14	
D	8.00-8.34	
E	8.70	

material obtained was not a mixture of the two bis-hydrogen phthaloyl derivatives was shown by the n.m.r. spectrum. Only one doublet was



XXXIVa

H	τ	J, cps
A	0.10	FG = 6
Aromatic	1.94-2.66	
B	4.00-4.40	
C	4.66-4.98	
D,E,F	5.34-6.40	
G	8.62	

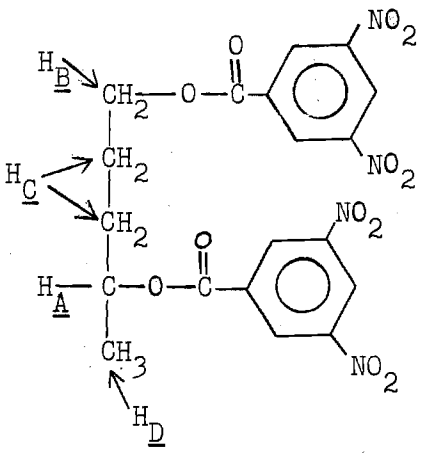
present in the region 8.00-9.00 τ. In a later preparation (77) of XXXIIIa and XXXIVa a crystalline mixture of the two materials was obtained, and the n.m.r. spectrum of this mixture clearly showed a doublet for the methyl group of each of the two diasterisomeric compounds. The infrared spectrum of the crystalline bis-hydrogen phthaloyl derivative (XXXIVa) was markedly different from the infrared spectrum of the

bis-hydrogen phthaloyl derivative of dl-3-nordihydrodideoxystreptose (XXXIIIa) that was obtained crystalline in a later preparation (100). The structure of XXXIIIa was established by a complete analysis of the n.m.r. spectrum of XXXIIIa. In addition, the melting points of the two bis-hydrogen phthaloyl derivatives were different. Because these bis-hydrogen phthaloyl derivatives were clearly different, the bis-hydrogen phthaloyl derivative, the n.m.r. spectrum of which is discussed directly above, was shown to be the bis-hydrogen phthaloyl derivative of dl-3-nor-4-epidihydrodideoxystreptose.

The mixture of dl-3-nordihydrodideoxystreptose (XXXIII), dl-3-nor-4-epidihydrodideoxystreptose (XXXIV), and 1,4-pentanediol (XLI) was treated with 3,5-dinitrobenzoyl chloride in pyridine. After chromatography of the reaction product over silicic acid, the bis-3,5-dinitrobenzoyl derivative of XLI (XLIb) was obtained crystalline as well as the bis-3,5-dinitrobenzoyl derivative of XXXIII (XXXIIIb).

The melting point observed for the bis-3,5-dinitrobenzoyl derivative of XLI was in agreement with the value recorded in the literature (58). Satisfactory analytical data were obtained for the compound, and the infrared and n.m.r. spectra were consistent for the expected structure. All of the absorptions in the n.m.r. spectrum of the compound were assigned and are shown below.

The bis-3,5-dinitrobenzoyl of XXXIII that was obtained crystalline showed no depression in melting point when mixed with a sample of this material obtained (78) in a later preparation. Satisfactory analytical data were obtained for the compound and the infrared spectra of the two samples were identical.

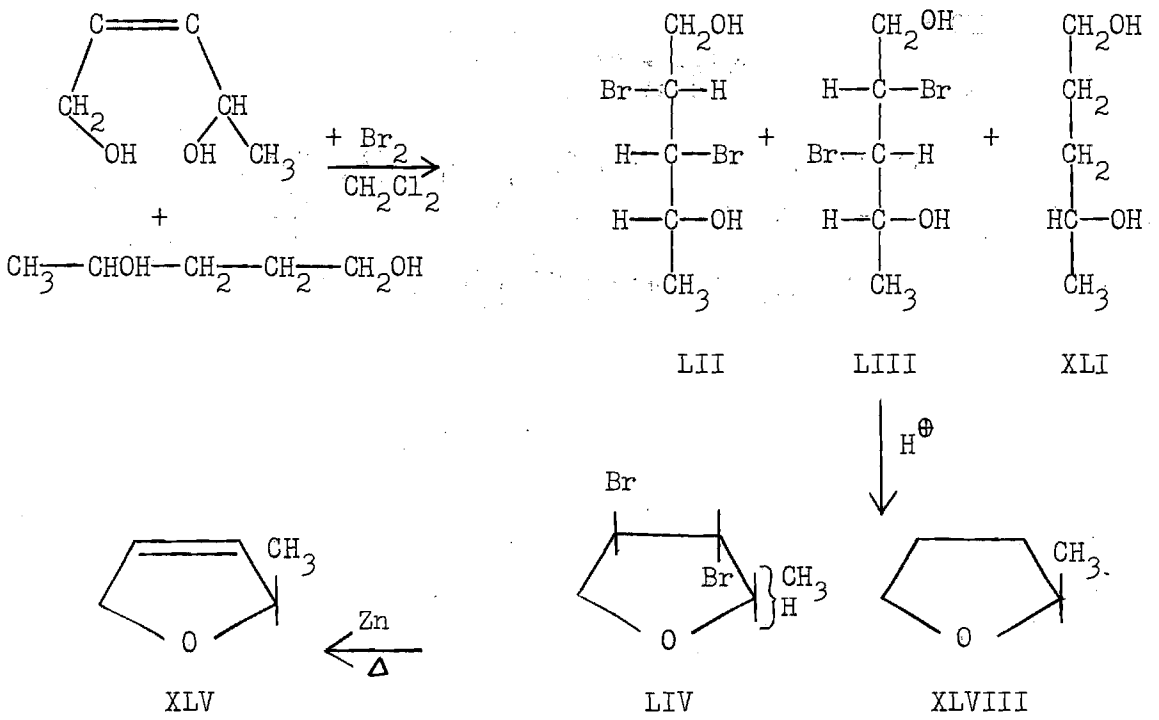


XLIb

H	τ	J, cps
Aromatic	0.64-0.88	AD = 6
A	4.34-5.00	
B	5.24-5.66	
C	7.66-8.28	
D	8.50	

Because of the difficulties encountered in the separation of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV) from 1,4-pentanediol (XLI) and the tedious methods required for the separation of the derivatives of XXXIII and XXXIV from the corresponding derivatives of XLI, another method for the preparation of 2,5-dihydro-2-methylfuran was attempted.

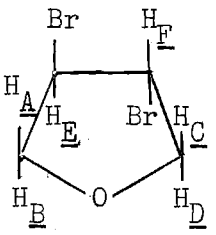
Since the acid catalyzed cyclization of the mixture of dl-5-deoxyribitol (XXXVII) and dl-5-deoxylyxitol (XXXVIII) furnished a mixture of XXXIII and XXXIV in good yield, it was anticipated that bromination of cis-2-pentene-1,4-diol (XL) and cyclization of the resulting mixture of dl-2,3,5-trideoxy-2,3-dibromoarabitol (LII) and dl-2,3,5-trideoxy-2,3-dibromoxylitol (LIII) should result in the formation of a mixture of diastereoisomeric 2-methyl-3,4-dibromotetrahydrofurans (LIV). Treatment of LIV with zinc dust was expected to regenerate a double bond and result in the formation of dl-2,5-dihydro-2-methylfuran (XLV). The 1,4-pentanediol (XLI), present as an impurity in the starting (XL) was expected to be cyclized to 2-methyltetrahydrofuran (XLVIII). Separation of LIV



from XL or XLI was anticipated by direct distillation.

cis-2-Butene-1,4-diol (XLIV) was chosen as a model compound for this reaction sequence. Addition of bromine to XLIV was carried out in methylene chloride solution at ice-bath temperature using equimolar amounts of XLIV and bromine. Cyclization of the dark sirup obtained, using p-toluenesulfonic acid as the acid catalyst, was carried out under water aspirator vacuum by heating the mixture in an oil bath. The resulting dl-3,4-trans-dibromotetrahydrofuran (LV) was distilled from the reaction mixture as fast as it was formed and was produced in 69% yield. This compound showed physical constants in agreement with the recorded (30) values. All of the absorptions in the n.m.r. spectrum of LV were assigned as shown below.

Debromination of LV was accomplished using zinc dust in isoamyl



LV

H	τ
A, B, C, D	5.22-5.58
E, F	5.68-5.98

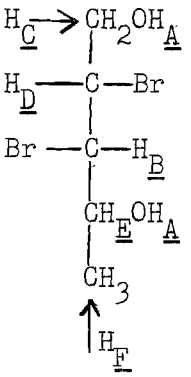
alcohol. The reaction was very exothermic and in order to control the reaction it was necessary to heat the mixture of zinc and isoamyl alcohol to the specified temperature, remove the source of heat, and add the solution of LV in isoamyl alcohol at a rate that maintained distillation of 2,5-dihydrofuran (XLVI).

The XLVI was formed in 84% yield based on the amount of LV used and in 58% yield based on the amount of cis-2-butene-1,4-diol (XLIV) used. The XLVI obtained showed physical constants in agreement with the literature (31) values and had an n.m.r. spectrum identical with that of an authentic sample.

Bromination of 2-pentene-1,4-diol was carried out in the same manner as the bromination of XLIV. When the addition of bromine was complete, the solution was concentrated and some crystalline material separated from the solution. Elemental analysis of this material was consistent for either of the expected diastereoisomeric products, dl-2,3,5-trideoxy-2,3-dibromoarabitol (LII) or dl-2,3,5-trideoxy-2,3-dibromoxylitol (LIII). The sirupy mixture of LII and LIII slowly evolved hydrogen bromide at room temperature but the crystalline compound, once purified, was stable.

The infrared and n.m.r. spectra were consistent for either structure. All of the absorptions in the n.m.r. spectrum were assigned and

are described below.

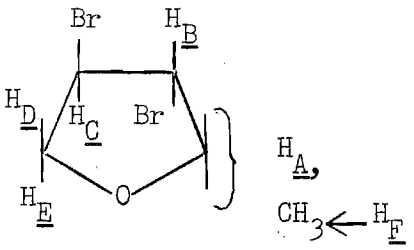


LII or LIII

H	τ	J, cps
A	3.43	EF = 5
B	4.97	BD = 7
C, D, E	5.40-6.08	BE = 7
F	8.48	

Cyclization of the mixture of dl-2,3,5-trideoxy-2,3-dibromoarabitol (LII), dl-2,3,5-trideoxy-2,3-dibromoxylitol (LIII) and 1,4-pentanediol (LI) was carried out in the manner described for the cyclization of dl-2,3-dibromobutane-1,4-diol (79). The mixture of 2-methyl-3,4-trans-dibromotetrahydrofurans (LIV) was produced in 63.5% yield, based on the amount of cis-2-pentene-1,4-diol in the starting material. The preparation showed infrared and n.m.r. spectra that were consistent for the expected structures. Elemental analysis of the mixture gave satisfactory analytical data for a mixture of the two epimeric 2-methyl-3,4-trans-dibromotetrahydrofurans (LIV). The infrared and n.m.r. spectra of the compound were consistent for the expected structure. The n.m.r. spectrum of LIV, which is described below, was complicated and no assignments except the position of absorption of H_F could be made. That both epimeric 2-methyl-3,4-trans-dibromotetrahydrofurans were present in the product was shown by the two doublets at 8.60 and 8.69 τ. The relative ratio of the two epimers was shown to be approximately 9:1 from the relative

intensities of the two doublets.

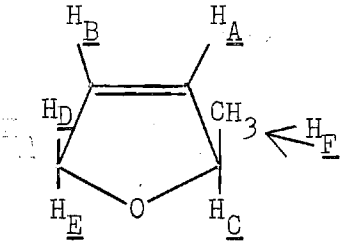


LIV

H	τ	J, cps
A, B, C, D, E	5.13-6.13	AF = 6
F	8.60 8.69	

Debromination of LIV was accomplished using zinc dust in n-hexyl alcohol by the method used for the debromination of dl-3,4-dibromotetrahydrofuran (LV). As in the debromination of LV, the reaction was very exothermic and the n-hexyl alcohol solution of LIV was added at a rate that maintained moderate distillation of 2,5-dihydro-2-methylfuran (XLV). The yield of XLV was 58.6% based on LIV, and 36.8% based on cis-2-pentene-1,4-diol (XLIII).

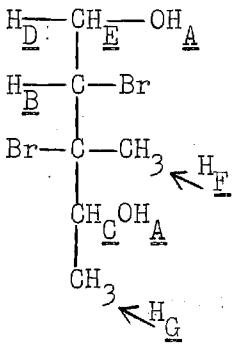
The physical constants observed for XLV were in agreement with the recorded (41) values, and the infrared and n.m.r. spectra were consistent with the expected structure. All the absorptions in the n.m.r. spectrum of XLV were assigned and are described below.



XLV

H	τ	J, cps
A, B	4.00-4.36	CF = 6
C	4.92-5.37	
D, E	5.39-5.58	
F	8.84	

Bromination of 3-methyl-cis-2-pentene-1,4-diol (XLIII) was carried out using the method described for the bromination of cis-2-butene-1,4-diol (XLIV). During the addition of the methylene chloride solution of bromine, the reaction mixture turned green, and crystalline material separated. This material amounted to a 22% yield of the addition product of bromine and XLIII . The remainder of the reaction product resisted crystallization. The infrared and n.m.r. spectra of the crystalline material were consistent for either of the expected diastereoisomeric dl-2,3,5-trideoxy-2,3-dibromo-3-C-methylarabitol (LVI) or dl-2,3,5-trideoxy-2,3-dibromo-3-C-methylxylitol (LVII). The crystalline compound gave satisfactory analytical data for either LVI or LVII. The n.m.r. spectrum of the compound could not be used to distinguish between the two possible structures. The absorptions present in the n.m.r. spectrum were assigned as shown below.

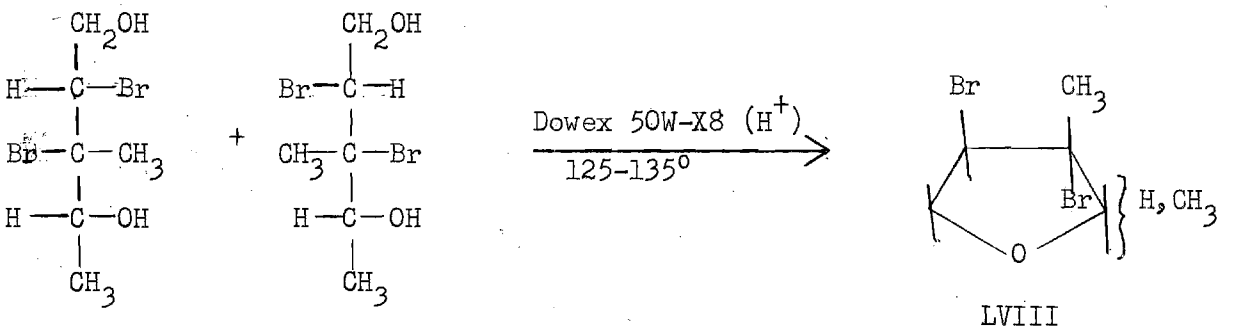


LVI or LVII

H	τ	J, cps
A	3.29	CG = 6
B	5.03	DB = 4.5
C	5.38	EB = 6.5
D,E	5.52-5.71	
F	7.98	
G	8.47	

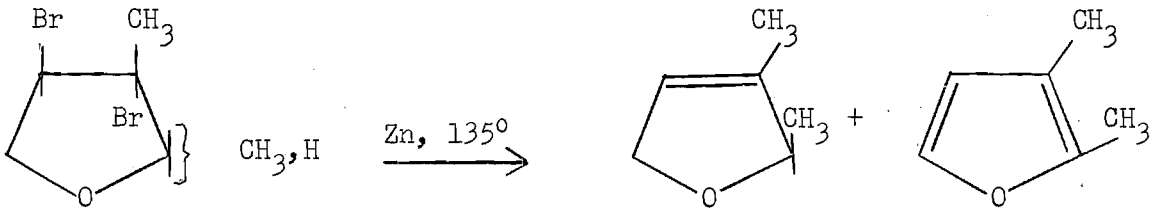
When the mixture of LVI and LVII was treated with Dowex 50W-X8 ion-exchange resin using the procedure previously described for the cyclization of dl-2,3-dibromobutane-1,4-diol (79), a 46.7% yield of 2,3-dimethyl-3,4-trans-dibromotetrahydrofurans (LVIII) was obtained. A large

quantity of black tar remained in the reaction vessel after the reaction was complete. The lower yield of this cyclization and the formation of polymeric material perhaps resulted because both the starting material and the product contain a relatively labile tertiary bromine atom. The



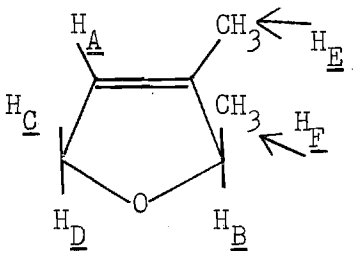
product from this reaction showed strong lachrymatory and vesicant properties. The product spontaneously evolved hydrogen bromide at room temperature, but could be stored without change for several days at -80°.

The debromination of the preparation (LVIII) using zinc dust in n-hexyl alcohol was performed using the procedure previously described (80) for the debromination of the mixture of trans-3,4-dibromo-2-methyltetrahydrofurans (LIV). The crude 2,5-dihydro-2,3-dimethylfuran (XVIII) was obtained in a yield of 79.5%. The n.m.r. spectrum of the crude product showed the presence of approximately five per cent of 2,3-dimethylfuran (XXI). This by-product presumably results from dehydrohalogenation, rather than dehalogenation, of the starting material. The crude product was purified by distillation using a lab-size spinning-band column; a 56.1% yield of pure 2,5-dihydro-2,3-dimethylfuran resulted. Elemental analyses were satisfactory for the expected formula and the infrared



LVIII XVIII XXI

and n.m.r. spectra were consistent for the expected structure. The absorptions present in the n.m.r. spectrum are assigned as shown below. Most of the absorptions present were too complicated to be analyzed. When the absorption resulting from the methyl group at highest field (H_F)



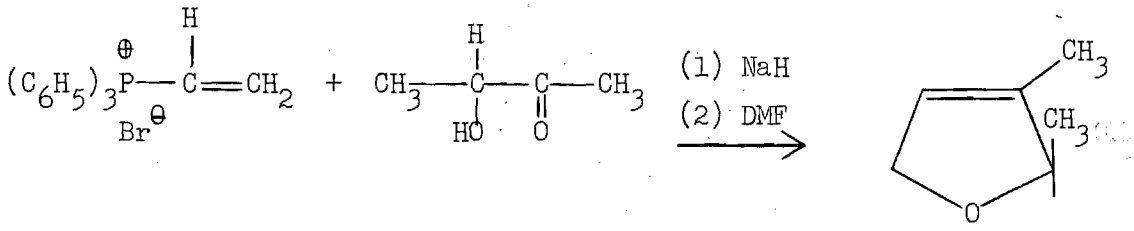
XVIII

H	τ	J, cps
A	4.50-4.68	BF = 6.0
B,C,D	5.20-5.67	
E	8.32	
F	8.83	

was expanded at 50 cps sweep width, the more intense member of the doublet was found to be split into a doublet that had J = 0.4 cps.

After the synthesis of 2,3-dimethyl-2,5-dihydrofuran (XVIII) by the route just described had been completed, a shorter and more convenient synthesis of XVIII was published (49). This synthesis consisted of the addition of vinyltriphenylphosphonium bromide to the anion of acetoin.

Several attempts were made to improve the reported yield (39%) for the synthesis. None resulted in a materially improved yield; the maximum yield obtained was 42%. Ethanol and benzene were observed as



XVIII

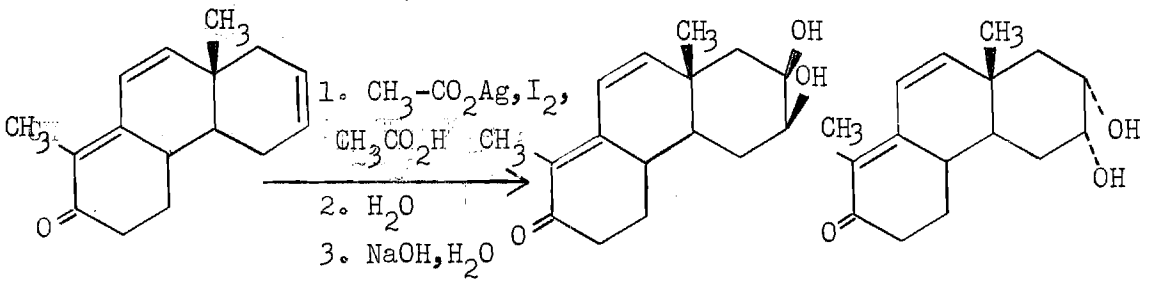
by-products present in the crude 2,3-dimethyl-2,5-dihydrofuran produced in this reaction. These products could only have resulted from side reactions involving the starting materials.

2,5-Dihydrofuran (XLVI) was chosen as a model for the cis-hydroxylation of 2,5-dihydro-2-methylfuran (XLV) and 2,5-dihydro-2,3-dimethylfuran (XVIII). cis-Hydroxylation of XLVI using the method of Milas and Sussman (72) (osmium tetroxide in a solution of hydrogen peroxide in t-butyl alcohol) resulted in a 24% yield of meso-3,4-dihydroxytetrahydrofuran (XXXII). A large quantity of polymeric material remained after distillation of the crude reaction product. Various modifications of this procedure gave poorer yields.

When the above hydroxylation procedure was used with 2,5-dihydro-2,3-dimethylfuran (XVIII), a 28.6% yield of a viscous black sirup resulted. GLC analysis of this preparation showed the presence of eight major components, two of which showed the same retention times as dl-dihydrodideoxystreptose (XIX) and dl-4-epidihydrodideoxystreptose (XX). Quantitative GLC analysis of the crude reaction mixture was performed using lauryl alcohol as an internal standard. The relative molar response of lauryl alcohol and XIX was determined to be 1.03. The yields of XIX and XX were determined to be 0.6% and 2.2%, respectively. The

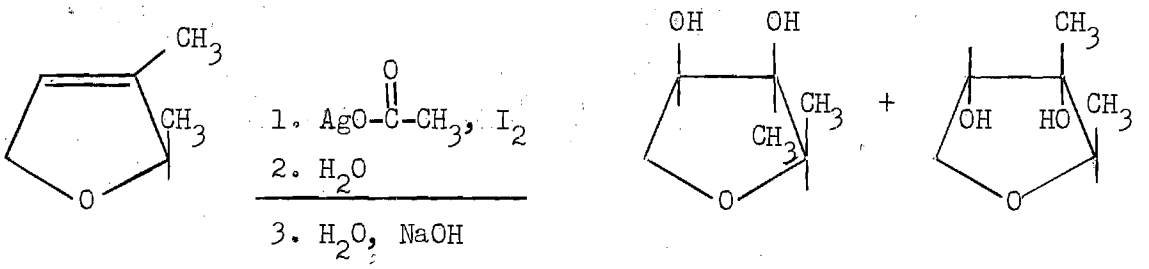
ratio of XX to XIX was 3.7:1. It was anticipated that XX would be formed in larger quantity than XIX, since the formation of XX corresponds to hydroxylation of XVIII from the less sterically hindered side. Since the yield was very low this method of hydroxylation was abandoned.

cis-Hydroxylation of the 6,7-double bond of dl-anti-trans-4,4a,5,8,8a-hexahydro-1,8a-dimethyl-2(3H) phenanthrone (LIX) using the silver acetate-iodine-wet acetic acid reagent, has been shown (71) to give the β-cis-diol (LX) in 71% yield and the α-cis-diol (LXI) in 2.5% yield. Osmium tetroxide hydroxylation of LIX has been shown to produce LXI as the major product and LX as the minor product.



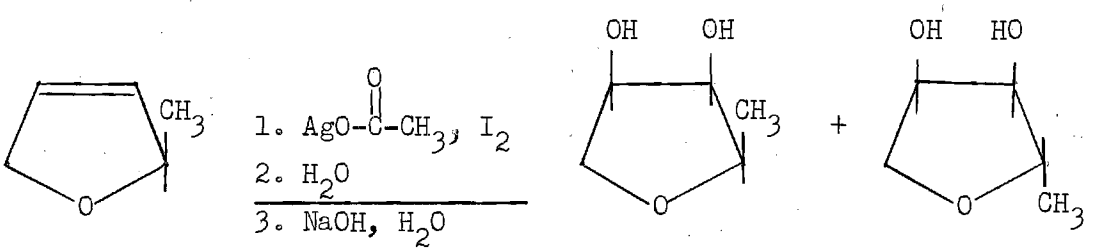
LIX LX LXI

Because hydroxylation by the silver acetate-iodine-wet acetic acid reagent takes place predominantly from the more sterically hindered side, and proceeds in good yield, it seemed promising as a method of hydroxylation of 2,5-dihydro-2,3-dimethylfuran (XVIII). dl-Dihydrodideoxystreptose (XIX), and not dl-4-epidihydrodideoxystreptose (XX), is the product that would result if hydroxylation of XVIII occurred predominantly from the more sterically hindered side of XVIII.



XVIII XIX (Major) XX (Minor)

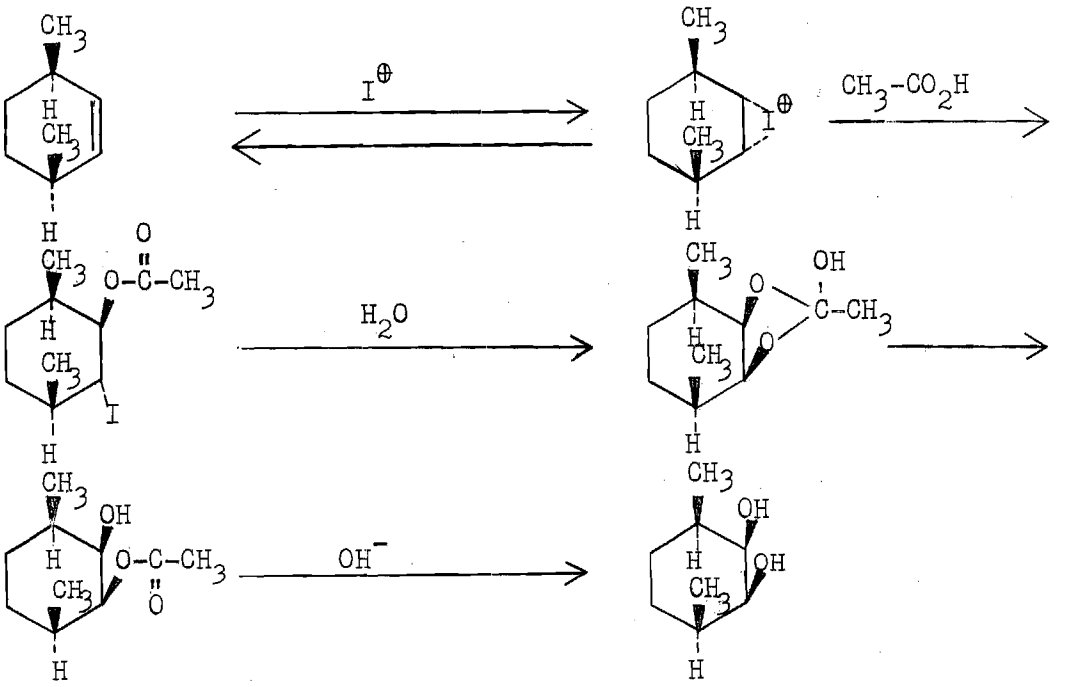
The hydroxylation of 2,5-dihydro-2-methylfuran (XLV) would also be expected to be somewhat stereospecific and to result in dl-3-nordihydrodideoxystreptose (XXXIII) as the major product and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV) as the minor product.



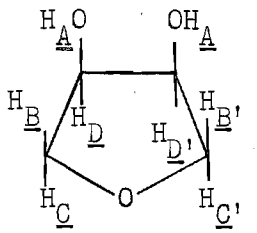
XLV XXXIII (Major) XXXIV (Minor)

The mechanism of silver acetate-iodine-wet acetic acid cis-hydroxylation has been formulated (71) as the initial attack of $I^{\oplus}$ from the less sterically hindered side of the molecule, followed by trans opening of the intermediate iodonium ion by acetic acid, and loss of a proton to give the iodoacetate. In the presence of water, displacement of iodide ion by the neighboring acetoxyl group results in the formation of the cis-orthoacetate. This intermediate is then hydrolyzed to give first the hydroxyacetate and then the diol. This mechanism is illustrated with cis-3,6-dimethylcyclohexene.

Hydroxylation of 2,5-dihydrofuran (XLVI) using the silver acetate-



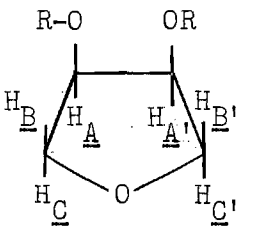
iodine-wet acetic acid reagent was first performed as a model reaction and resulted in a 68% yield of meso-3,4-dihydroxytetrahydrofuran (XXXII). This compound showed physical constants that were in agreement with the recorded (33) values and had an n.m.r. spectrum that was consistent with the expected structure. The absorptions in the n.m.r. spectrum were assigned as shown below.



XXXII

H	τ
A	5.23
B, B', C, C', D, D'	5.57-6.42

Treatment of XXXII with benzoyl chloride in pyridine furnished a 90.5% yield of meso-3,4-dibenzoyloxytetrahydrofuran (LXII). This crystalline compound gave analytical data that were satisfactory for the expected formula. The infrared and n.m.r. spectra were consistent for the expected structure. The absorptions present in the n.m.r. spectrum are assigned as shown below.



LXII R = C_6H_5-C-

H	τ
Aromatic	1.92-2.25 and 2.41-3.00
AA'	4.18-4.59
BB',CC'	5.60-6.63

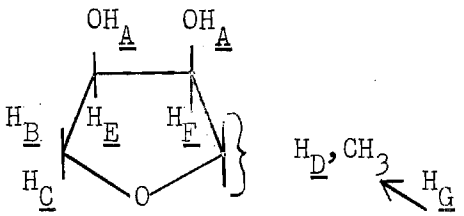
Hydroxylation of olefins by neutral aqueous potassium permanganate has been shown (81) to result in the cis-orientation of the hydroxyl groups; the yields are frequently good. Accordingly, cis-hydroxylation of 2,5-dihydrofuran (XLVI) using this reagent was investigated.

cis-Hydroxylation of XLVI was accomplished in 47.6% yield using cold aqueous potassium permanganate. Addition of magnesium sulfate to the reaction mixture to keep the mixture from becoming basic did not improve the yield. The physical constants obtained for the resulting meso-3,4-dihydroxytetrahydrofuran (XXXII) prepared by this method were in agreement with the recorded values (33).

Because cis-hydroxylation of 2,5-dihydrofuran (XLVI) using the silver acetate-iodine-wet acetic acid reagent gave a better yield of meso-3,4-dihydroxytetrahydrofuran than was obtained when potassium

permanganate was used, the former reagent was used for the hydroxylation of 2,5-dihydro-2-methylfuran (XLV). This method of cis-hydroxylation was also favored because hydroxylation was expected to occur predominantly in the formation of dl-3-nordihydrodideoxystreptose (XXXIII) as the major product.

cis-Hydroxylation of XLV by this method resulted in a 79.7% yield of a sirup (LXV) that presumably was a mixture of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV). This sirup gave analytical data that were satisfactory for the expected formula. The infrared and n.m.r. spectra of the preparation were consistent for the expected product. The absorptions present in the n.m.r. spectrum of LXV were assigned as shown below.

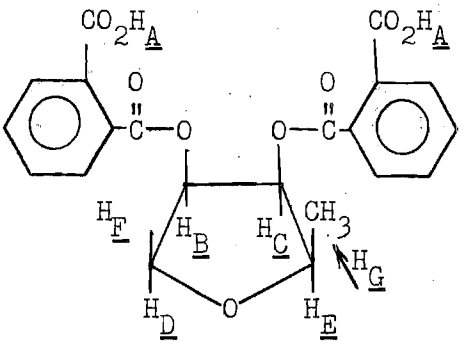


LXV

H	τ	J, cps
A	5.31	DG = 6
B, C, D, E, F	5.56-6.63	
G	8.76	

Two epimeric diols (XXXIII and XXXIV) would be expected to be produced, in different yields, from this hydroxylation procedure. The n.m.r. spectrum of the product obtained showed only one doublet in the region 8.00-9.00 τ. In addition, the preparation gave only one peak by GLC analysis. That this preparation actually consisted of the two epimeric diols was shown by the preparation of certain derivatives of this particular preparation, and also derivatives of a corresponding diol mixture prepared by potassium permanganate hydroxylation (77).

Treatment of this diol mixture with phthalic anhydride in pyridine resulted in a 72% yield of crystalline material that gave satisfactory analytical data for the bis-hydrogen phthaloyl derivative of dl-3-nor-dihydrodideoxystreptose (XXXIII). This phthaloyl derivative had infrared and n.m.r. spectra that were consistent for the expected structure. The n.m.r. spectrum of this compound was particularly definitive, and the coupling constants for all of the ring protons could be determined by first order analysis. These data are enumerated below.



XXXIIIa

H	τ	J, cps
Aromatic	2.00-2.61	BC = 5.6
A	2.71	BD = 5.5
B	4.29	BF = 3.9
C	4.88	CE = 7.4
D	5.61	EG = 6.3
E	5.89	FD = -10.2
F	6.02	
G	8.63	

A mixture of the epimeric bis-hydrogen phthaloyl derivatives of XXXIII and XXXIV was obtained (82) in a later preparation, and the n.m.r. spectrum of that preparation clearly showed the presence of two doublets in the 8.00-9.00 τ region. Because the n.m.r. spectrum of the phthaloyl derivative of the diol preparation resulting from the silver acetate-iodine-wet acetic acid hydroxylation showed only one doublet in the region 8.00-9.00 τ for the methyl group, this derivative is not a mixture of the bis-hydrogen phthalates of XXXIII and XXXIV.

Since the magnitude of the coupling constant J_{CE} is 7.4 cps, these

two ring protons (H_C and H_E) are clearly cis (83). Therefore the bis-hydrogen phthalate (LXXIVa) obtained pure from this preparation is that derived from dl-3-nordihydrodideoxystreptose (XXXIII).

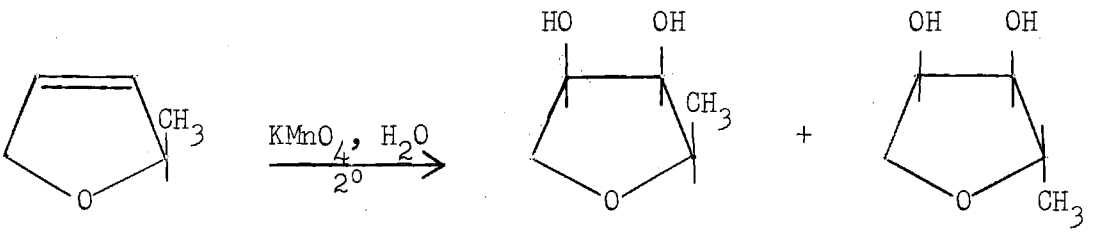
Because a 72% yield of the bis-hydrogen phthaloyl derivative of dl-3-nordihydrodideoxystreptose (XXXIII) was obtained, hydroxylation of 2,5-dihydro-2-methylfuran using the silver acetate-iodine-wet acetic acid reagent must proceed to an extent of at least 72% from the more sterically hindered side. This result is expected, since hydroxylation of olefins using the silver acetate-iodine-wet acetic acid reagent has been shown (71) to result in hydroxylation from the more sterically hindered side.

A more detailed discussion of the conformation of the bis-hydrogen phthaloyl derivative of XXXIII and other related compounds appears at the end of Chapter III of this thesis.

Since optical resolution of synthetic dl-dihydrodideoxystreptose was desired for the complete synthetic proof of structure, an attempt to resolve dl-3-nordihydrodideoxystreptose (XXXIII), as a model, was made. Partial optical resolution of XXXIII was accomplished by fractional crystallization of the brucine salt of the bis-hydrogen phthaloyl derivative. From the brucine salt that resulted from the third recrystallization, a dextrorotatory phthaloyl derivative was obtained that showed $[\alpha]_D$ 44.0° + 0.6°. The filtrates from the fractional crystallization of the salt resisted crystallization. No further attempt was made to obtain the levorotatory phthalate.

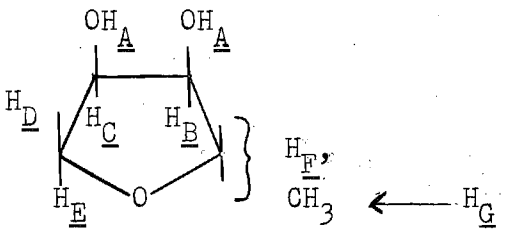
Even though hydroxylation of 2,5-dihydro-2-methylfuran (XLV) using the silver acetate-iodine-wet acetic acid reagent produced dl-3-nordihy-

drodideoxystreptose (XXXIII) in largest amount, an investigation of the hydroxylation of 2,5-dihydro-2-methylfuran (XLV) using aqueous potassium permanganate was undertaken. This reaction proceeded in 52% yield, and gave a mixture of diols (XXXIII and XXXIV). The diol mixture obtained,



XLV XXXIII XXXIV

a distillable sirup, had analytical data that were satisfactory for the formula of the two expected epimers. The preparation had infrared and n.m.r. spectra that were consistent for a mixture of the resulting diols. The absorptions in the n.m.r. spectrum are described below.



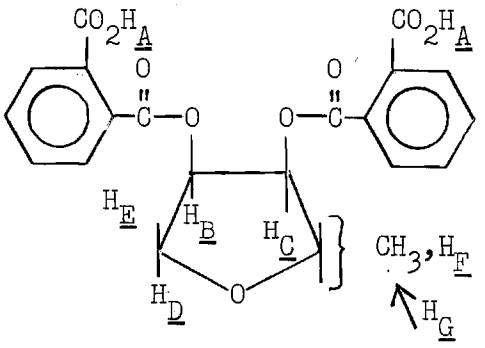
XXXIII + XXXIV

H	τ	J, cps
A, B, C, D, E, F	5.43-6.54	FG = 6
G	8.73	

As was the case with the diol mixture resulting from the hydroxylation of 2,5-dihydro-2-methylfuran (XLV) using the silver acetate-iodine-wet acetic acid reagent, the n.m.r. spectrum of this diol mixture showed only one doublet resulting from the methyl group at 8.73 τ and GLC analysis showed only one peak.

This preparation was treated with phthalic anhydride in pyridine.

The resulting mixture of bis-hydrogen phthaloyl derivatives was obtained crystalline after chromatography over silicic acid. The n.m.r. spectrum of the preparation, after two recrystallizations, showed two doublets in the region 8.00-9.00 τ. The absorptions in the n.m.r. spectrum were assigned as shown below. The infrared spectrum of the mixture was con-

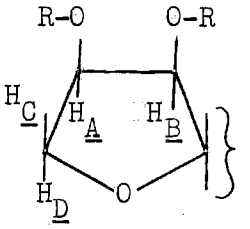


H	τ	J, cps
Aromatic	2.00-2.68	FG = 6
A	3.19	
B	4.16-4.50	
C	4.75-5.08	
D,E,F	5.46-6.41	
G	8.65 and 8.75	

sistent for the expected structures.

When the mixture of dl-3-nordihydrodideoxystreptose (XXXIII) and dl-3-nor-4-epidihydrodideoxystreptose (XXXIV) was treated with p-nitrobenzoyl chloride in pyridine, a mixture of crystalline bis-p-nitrobenzoyl derivatives of XXXIII and XXXIV was obtained. The mixture LXVI showed m.p. 95-104° when initially crystallized, but after three crystallizations the melting point was 96.5-119.5°. The broadening of the melting point range after three crystallizations indicated that the original crystalline mixture of epimers was becoming enriched in the epimer that was originally present in smallest amount. The analytical data obtained for the mixture was satisfactory for the expected molecular formula and the infrared spectrum of the mixture was consistent with the expected structures.

The n.m.r. spectrum of the preparation was consistent for a mixture of the epimeric bis-p-nitrobenzoates of XXXIII and XXXIV. The absorptions present in the n.m.r. spectrum were assigned as shown below.



$H_E, CH_3 \leftarrow H_F$

$R = p\text{-}NO_2\text{-}C_6H_4\overset{O}{\overset{\|}{C}}-$

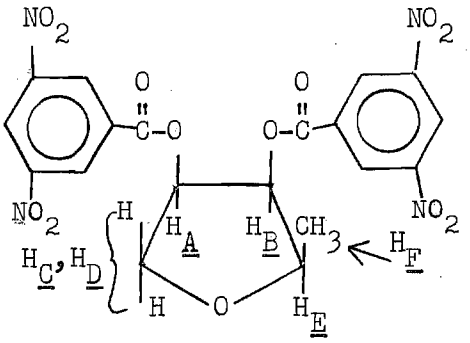
LXVI

H	τ	J, cps
Aromatic	1.60-2.10	EF = 6
A	4.05-4.50	
B	4.58-4.92	
C,D,E	5.30-6.10	
F	8.54 and 8.59	

The fact that the n.m.r. spectrum of the preparation showed two doublets in the region 8.50-8.60 τ resulting from the methyl groups present in the two compounds indicated that both epimers were present. This also indicates that, as previously mentioned, the diol resulting from potassium permanganate hydroxylation was also a mixture of the two epimers, even though the n.m.r. spectrum of this mixture showed only one doublet resulting from the methyl group, and GLC analysis indicated only one component. The relative ratio of the two epimeric bis-p-nitrobenzoyl derivatives in the material that had been recrystallized two times was approximately 1.4:1 as determined from the relative intensities of the two doublets at 8.54 and 8.59 τ in the n.m.r. spectrum of the preparation.

When the mixture of diols (XXXIII and XXXIV) was treated with 3,5-dinitrobenzoyl chloride, one of the two epimeric bis-3,5-dinitrobenzoyl derivatives was obtained pure. This crystalline derivative was identical with a sample obtained in another way (43), as shown by the fact that

the two samples had superimposable infrared spectra, and there was no depression in mixture melting point. The n.m.r. spectrum of the compound showed only one doublet in the region 8.00-9.00 τ, which indicated that only one of the two possible epimers was present. The absorptions present in the n.m.r. spectrum were assigned as described below.



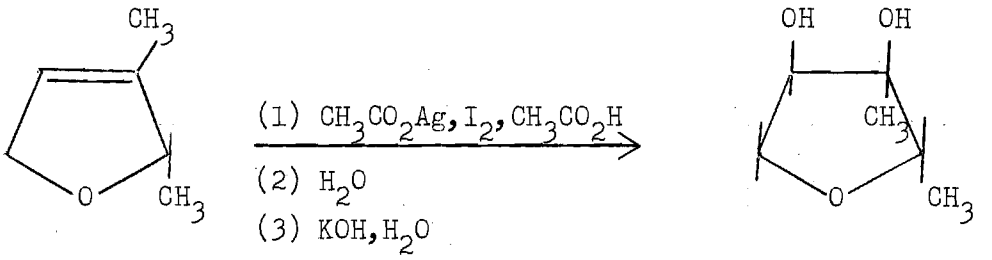
H	τ	J, cps
Aromatic	0.64-1.18	AB = 6
A	4.03-4.39	BE = 6
B	4.63	EF = 6.2
C, D, E	5.26-6.18	
F	8.62	

That this derivative is the 3,5-dinitrobenzoyl derivative of dl-3-nordihydrodideoxystreptose is shown by the pattern of H_B in the n.m.r. spectrum. The absorption resulting from H_B is a triplet that has J = 6 cps. It is known that H_A and H_B are cis, and therefore H_B and H_E must also be cis. If H_B were trans to H_E a completely different pattern would be expected for H_B; a closely spaced quartet having $J_{BE} \leq 3$ cps would be anticipated.

In an attempt to purify and possibly resolve this mixture of diols (XXXIII and XXXIV), the mixture was treated with l-menthoxyacetyl chloride. The resulting sirup showed an infrared spectrum that was consistent for the expected mixture, but the sirup resisted crystallization even after chromatography over silicic acid.

After the model hydroxylations of 2,5-dihydrofuran (XLVI) and

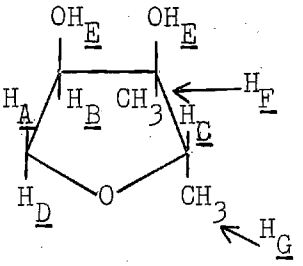
2,5-dihydro-2-methylfuran (XLV) were complete, the hydroxylation of 2,5-dihydro-2,3-dimethylfuran (XVIII) was performed using the silver acetate-iodine-wet acetic acid reagent and the conditions employed in the hydroxylation of 2,5-dihydro-2-methylfuran by this method. The crude reaction product consisted of a viscous black sirup that resisted crystallization. Chromatography of the sirup over silicic acid furnished several initial fractions of black tar and then one sirupy fraction that furnished a 19.8% yield of dl-4-epidihydrodideoxystreptose after crystallization from isopropyl ether.



XVIII XX

Sublimation of the resulting brown crystalline material in vacuo furnished a 14.3% yield of white, hygroscopic dl-4-epidihydrodideoxystreptose (XX). The pure compound had analytical data that were consistent for the molecular formula and an infrared spectrum consistent for the expected structure. The infrared spectrum was markedly different from the infrared spectrum of authentic L-dihydrodideoxystreptose (XIII) derived from streptomycin. The n.m.r. spectrum of XX was consistent for the expected structure but very different in the signal pattern of the ring protons from the n.m.r. spectrum of XIII. The n.m.r. spectrum of dl-4-epidihydrodideoxystreptose (XX), recorded using a 60 Mc. instrument,

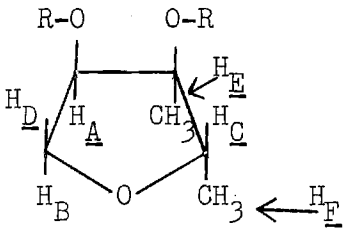
is given as Fig. 2. Considerable difficulty was experienced in analyzing the spectrum. Finally, with the aid of a spectrum determined at 100 Mc. (86), the experimental spectrum was matched with a calculated spectrum (84). The data are given below.



XX

H	τ	J, cps	
A	5.89	AB =	3.25
B	6.18	AD =	-10.00
C	6.22	BD =	5.25
D	6.35	CG =	6.30
E	6.67		
F	8.85		
G	8.85		

Treatment of dl-4-epidihydrodideoxystreptose with an excess of p-nitrobenzoyl chloride in hot pyridine furnished, after chromatography over aluminia, a 40.7% yield of a crystalline bis-p-nitrobenzoyl derivative (LXXIV). The compound gave satisfactory analytical data for the expected formula, and the infrared and n.m.r. spectra were consistent for the expected product. All the absorptions in the n.m.r. spectrum of the compound were assigned as shown below.



LXXIV

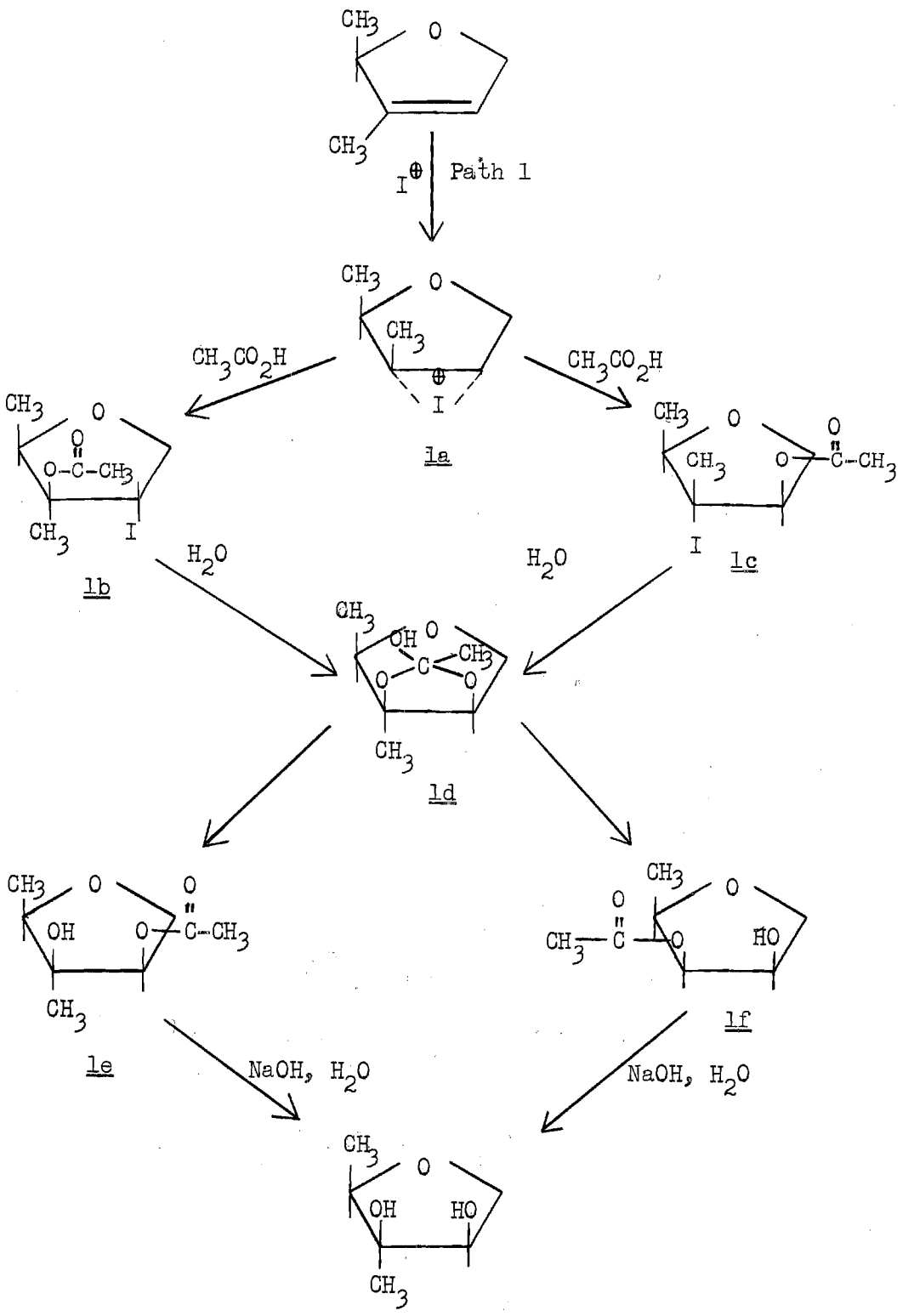
R = p-NO_2-C_6H_4-C(=O)-

H	τ	J, cps	
Aromatic	1.89	AB =	5.2
A	4.21	AD =	2.2
B	5.55	BD =	-11.5
C	5.61	CF =	6.4
D	6.02		
E	8.35		
F	8.56		

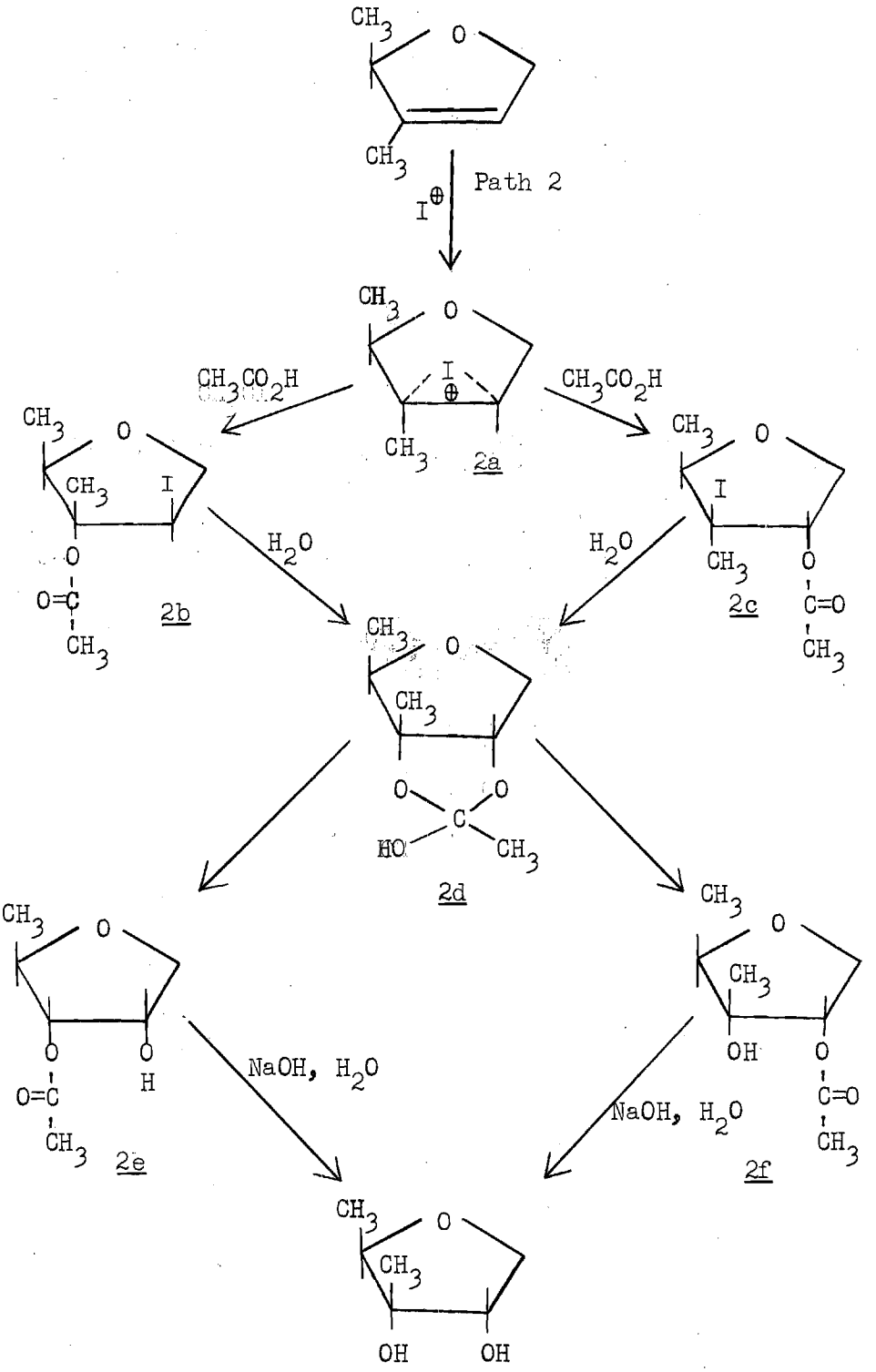
The fact that hydroxylation of 2,3-dihydro-2,3-dimethylfuran using the silver acetate-iodine-wet acetic acid reagent gave only dl-4-epidihydrodideoxystreptose (XX), and no dl-dihydrodideoxystreptose (XIX), is worthy of comment. The product analysis (by GLC), which showed only one volatile component and the low yield obtained, are in distinct contrast with the results of hydroxylation of 2,5-dihydro-2-methylfuran. In the latter case a yield of about 80% of diols resulted, and of this amount a minimum of 72% was dl-3-nordihydrodideoxystreptose. This result was anticipated, since hydroxylation by this procedure produces in major amount the diol corresponding to hydroxylation from the more sterically hindered side.

The reaction pathways for 2,5-dihydro-2,3-dimethylfuran are shown below. Reaction of 2,5-dihydro-2,3-dimethylfuran with $I^{\oplus}$ would be expected to result in the preferential formation of 1a over 2a since attack of $I^{\oplus}$ would be expected to take place predominantly from the less sterically hindered side of the molecule. Reaction of the intermediate iodonium ion 1a with acetic acid, the active nucleophile, would result in the formation of 1b and 1c after the loss of a proton. The latter would be expected to predominate because S_N2 solvolysis at the secondary carbon would be expected to predominate over S_N2 solvolysis at the tertiary position. Although the carbon atom at C_3 of the tetrahydrofuran ring probably has a considerable amount of carbonium ion character, no epimerization at this center takes place because no trans-diol is observed in the crude product.

The intermediate 1c, a tertiary iodide, may not be particularly stable under the reaction conditions (90-95° in glacial acetic acid for



XIX


Path 2
$I^{\oplus}$
CH_3CO_2H
CH_3CO_2H
H_2O
H_2O
NaOH, H_2O
NaOH, H_2O
2a
2b
2c
2d
2e
2f
XX

3 hrs.), and is probably consumed by side reactions. The low yield of diol, but not the exclusive formation of dl-4-epidihydrodideoxystreptose (XX), may be accounted for by the formation of a large amount of tar and resinous products that possibly result from decomposition of the intermediate tertiary iodides.

The next step in the reaction mechanism is the formation of the cis-orthoacetate 1d by the reaction of 1b and 1c with water. Because of the large amount of steric hindrance present in the molecule owing to the presence of the orthoacetate group on the same side of the ring as the C_2 methyl group, the energy of activation for the formation of 1d will necessarily be large, and perhaps insurmountable under the reaction conditions.

The formation of the only observed product of the reaction, dl-4-epidihydrodideoxystreptose, requires attack of $I^{\oplus}$ on 2,5-dihydro-2,3-dimethylfuran from the more sterically hindered side and the formation of the intermediate iodonium ion 2a. Although the formation of 2a is less favored than the formation of 1a, the conversion of 2a, once formed, to the required 2d would be energetically much more favorable than the conversion of 1a to 1d, since 1d is much more sterically hindered than 2d. The conversion of 2d to the observed product, XX, would be expected to proceed without difficulty in the presence of aqueous methanolic sodium hydroxide.

Hydroxylation of 2,5-dihydro-2,3-dimethylfuran (XVIII) using cold, aqueous potassium permanganate was performed using the previously described procedure for the hydroxylation of 2,5-dihydrofuran (XLVI) and 2,5-dihydro-2-methylfuran (XLV). GLC analysis of the crude reaction

product, a dark sirup, showed the presence of two volatile compounds that had retention times of 7.40 and 8.80 min. and were present in a ratio of 1:3.4, respectively. Under identical conditions authentic L-dihydrodideoxystreptose had a retention time of 7.40 min. and dl-4-epidihydrodideoxystreptose had a retention time of 8.80 min.

These results clearly show that the minor product of this reaction is dl-dihydrodideoxystreptose, as expected, since cis-hydroxylation using potassium permanganate is known (81) to proceed predominantly from the less sterically hindered side of the double bond.

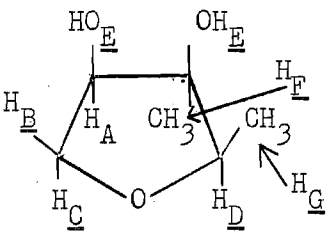
The sirup obtained as the crude reaction product in this hydroxylation resisted crystallization from a variety of solvents. Chromatography of the sirup over silicic acid furnished a 48.5% yield of a sirup that was shown by GLC analysis to contain only dl-dihydrodideoxystreptose (XIX) and dl-4-epidihydrodideoxystreptose (XX). Assuming the relative molar response of XIX and XX are the same, the chromatographed material consisted of 22.6% of XIX and 77.4% of XX, as shown by integration of the areas under the peaks.

Separation of XIX and XX was accomplished by fractional crystallization of the chromatographed sirup from dry isopropyl ether. A solution of the sirup in dry isopropyl ether was seeded with crystalline dl-4-epidihydrodideoxystreptose (XX), and after crystallization was complete, the crystalline material was removed by filtration. Crystalline dl-dihydrodideoxystreptose (XIX) was then obtained from the filtrate with difficulty. Once seed crystals of each of the two epimers were available, no difficulty was encountered in the fractional crystallization. Based on the amount of 2,5-dihydro-2,3-dimethylfuran used in the hydroxylation,

the yields of purified, crystalline XIX and XX were 11.7% and 22.7%, respectively. An additional quantity of each epimer could be obtained after rechromatography of the combined filtrates, followed by fractional crystallization.

The dl-dihydrodideoxystreptose (XIX) obtained in the above way had analytical data that were consistent with the expected formula. The infrared and n.m.r. spectra of synthetic dl-dihydrodideoxystreptose (XIX) were identical with the corresponding spectra of an authentic sample of L-dihydrodideoxystreptose (XIII) derived from streptomycin. The melting points of XIX and XIII were different, but it is well known (85) that a racemate can melt lower, at the same temperature, or higher than one of the optically pure enantiomers.

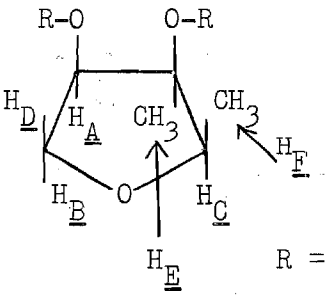
The n.m.r. spectrum of dl-dihydrodideoxystreptose (XIX), recorded using a 60 Mc. instrument is given as Fig. 3. The analysis of this spectrum was difficult; however, with the aid of a spectrum determined at 100 Mc. (86), the experimental spectrum was finally matched with a computed spectrum (84). The parameters used are given below.



XIX

H	τ	J, cps	
A	5.98	AB =	4.90
B	6.09	AC =	7.00
C	6.34	BC =	-8.75
D	6.36	DG =	6.30
E	6.98		
F	8.78		
G	8.79		

When dl-dihydrodideoxystreptose (XIX) was treated with an excess of p-nitrobenzoyl chloride in pyridine, a crystalline bis-p-nitrobenzoyl derivative (LXVII) was obtained in 46.8% yield after chromatography over aluminia. The compound gave analytical data that were satisfactory for the expected formula. The infrared and n.m.r. spectra were consistent for the expected product. All the absorptions in the n.m.r. spectrum were assigned and are described below.

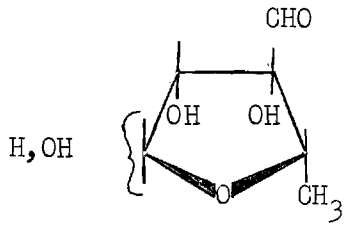


R = p-NO_2-C_6H_4-C(=O)-

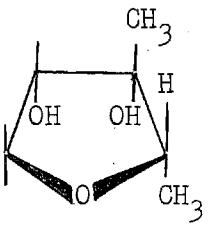
LXVII

H	τ	J, cps
Aromatic	1.64-2.08	
A	4.24	AB = 4.9
B	5.70	AD = 2.9
C	5.72	BD = -11.1
D	5.88	CF = 6.6
E	8.16	
F	8.50	

The recently reported, stereospecific total synthesis of L-streptose (XVI) (25) has confirmed the absolute stereochemistry at C_2 and C_4 of L-streptose (XVI) as well as L-dihydrodideoxystreptose (XIII).



XVI



XIII

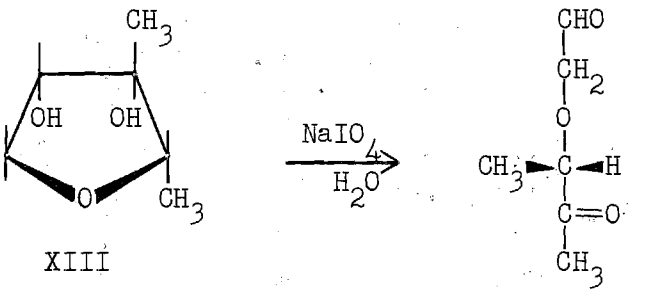
The synthesis of streptose did not unequivocally prove that the C_2-C_3 hydroxyl groups were cis, as was assigned in the original work. Cold aqueous potassium permanganate hydroxylation of 2,5-dihydro-2,3-

dimethylfuran (XVIII) furnished two cis-diols, dl-dihydrodideoxystreptose (XIX) and dl-4-epidihydrodideoxystreptose (XX). One of these diols had identical infrared and n.m.r. spectra and identical GLC behavior when compared with an authentic sample of L-dihydrodideoxystreptose. Therefore, the C_2-C_3 hydroxyl groups of L-dihydrodideoxystreptose, as well as those of L-streptose, are proved to be cis, and the structures initially assigned to these compounds are shown to be correct.

The synthetic procedures described produced the racemate of dihydrodideoxystreptose. In order to enhance the value of this synthetic work, it seemed desirable to effect the optical resolution of dl-dihydrodideoxystreptose and to make a direct comparison of the resolved compound with an authentic sample of L-dihydrodideoxystreptose derived from streptomycin.

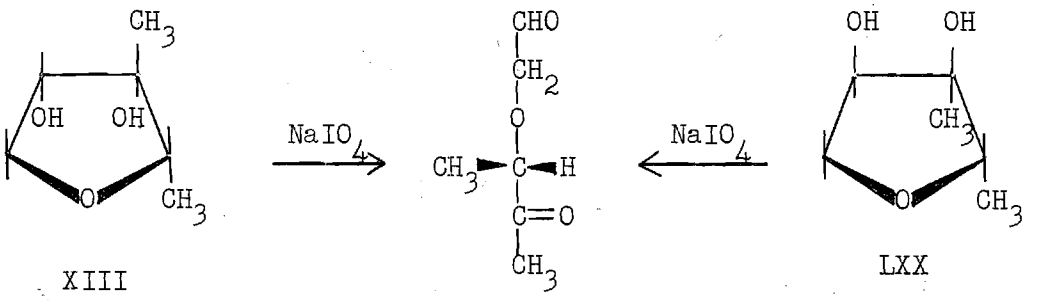
It is worthy of comment that, if the optical resolutions of dl-dihydrodideoxystreptose (XIX) and dl-4-epidihydrodideoxystreptose (XX) could be achieved, the absolute stereochemistry of all of the centers of all four compounds could be established by a relatively simple experiment. The syntheses that have been described have unequivocally established the absolute stereochemistries of the carbon atoms of L-dihydrodideoxystreptose; the absolute stereochemistry at C_4 is L. If a solution of L-dihydrodideoxystreptose (XIII) and one equivalent of sodium metaperiodate were placed in a polarimeter tube, the optical rotation observed would be expected to approach a value resulting from compound LXVIII.

If either optically active D-4-epidihydrodideoxystreptose (LXIX) or L-4-epidihydrodideoxystreptose (LXX) were reacted similarly, the optical rotation of the solution would be either identical or of the same



XIII LXVIII

magnitude but opposite direction to that obtained from L-dihydrodideoxystreptose (XIII). These reactions are illustrated by the following equations. Thus, the optical resolutions of dl-dihydrodideoxystreptose (XIX)

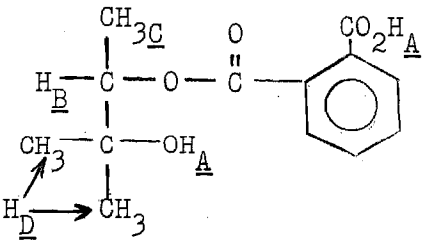


XIII LXVIII LXX

and dl-4-epidihydrodideoxystreptose (XX) were deemed advisable.

It has been stated that "glycols cannot be resolved by the phthalic ester procedure because they tend to form polymeric esters instead of simple hydrogen phthalates when treated with phthalic anhydride" (87). Nevertheless, because of the successful preparation of the bis-hydrogen phthaloyl derivative of 3-nordihydrodideoxystreptose (XXXIII) and successful partial optical resolution of this derivative by fractional crystallization of the brucine salt, this method of resolution of dl-dihydrodideoxystreptose (XIX) was attempted.

As a model compound for the preparation of a mono-hydrogen phthaloyl derivative of a 1,2-glycol containing secondary and tertiary hydroxyl groups, 3-methyl-2,3-butanediol was chosen. A crystalline 3-hydrogen phthaloyl derivative (LXXI) of this compound was prepared in 92.6% yield. The derivative gave satisfactory analytical data and had n.m.r. and infrared spectra that were consistent with the expected formula. The absorptions present in the n.m.r. spectrum were assigned as shown below.



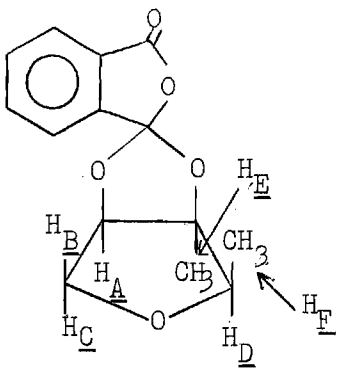
LXXI

H	τ	J, cps
A	1.32	BC = 6.5
Aromatic	2.00-2.58	
B	4.74	
C	8.70	
D	8.70	

Because the preparation of a mono-hydrogen phthaloyl derivative of a diol containing secondary and tertiary hydroxyl groups had been shown to be successful, and because the partial resolution of the bis-hydrogen phthaloyl derivative of dl-3-nordihydrodideoxystreptose (XXXIII) was successful, this method of resolution of dl-dihydrodideoxystreptose was attempted.

The reaction of dl-dihydrodideoxystreptose (XIX) with phthalic anhydride in hot pyridine, followed by the standard workup, gave a 76% yield of a brown glass. The brown glass was chromatographed over silicic acid. Initial fractions from the silicic acid chromatography gave, in 8% yield, a crystalline, pure material. The analytical data that were obtained were consistent for the formula $C_{14}H_{14}O_5$, rather than the formula $C_{14}H_{16}O_6$, which is the formula for a mono-hydrogen phthaloyl derivative of dl-dihy-

drodideoxystreptose. The infrared spectrum showed only one absorption (5.60 μ) in the 5.00-6.00 μ region when recorded as a liquid film whereas the mono-hydrogen phthaloyl derivative of 2,3-butanediol (LXXI) showed absorptions at 5.66 and 5.81 μ, and the bis-hydrogen phthaloyl derivative of dl-3-nordihydrodideoxystreptose showed absorptions at 5.82 and 5.90 μ. Based on the analytical results and the infrared spectrum, this crystalline compound would appear to be the phthalide (LXXII). The carbonyl group of phthalide itself is reported to absorb near 5.56 μ, and the carbonyl group of 3-methylenephthalide near 5.61 μ (88). Because the spirocyclic carbon atom of LXXII is asymmetric, the crystalline material obtained could have been either of the two possible epimers. The n.m.r. spectrum of the compound was also consistent with this structural formula, and was completely analyzed. The data are given below.



LXXII

H	τ	J, cps
Aromatic	2.10-2.40	AB = 0
A	5.18	AC = 3.25
B	5.85	BC = -11.3
C	6.35	DF = 6.31
D	6.45	
E	8.38	
F	8.68	

Later chromatography fractions had n.m.r. spectra that appeared reasonable for the impure 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose. These fractions could not be crystallized, and TLC analysis showed that at least five compounds were present in these fractions. One of these impurities was phthalic acid, and one was the

phthalide (LXXII). The column fractions that appeared to be richest, by their n.m.r. spectra and TLC analysis, in the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose were pooled and treated with brucine. No crystalline material could be obtained.

Modification in the preparation of the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose, for example omitting heating, or omitting workup with acid, gave results that were similar to the above.

Preparative TLC of a fraction presumably rich in the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose gave a preparation that still showed three spots upon analytical TLC analysis.

A fraction that was presumably rich in the 2-hydrogen phthaloyl derivative of dihydrodideoxystreptose was heated under reflux for four days with chloroform that contained five per cent acetic acid. TLC analysis showed that the spot presumably corresponding to the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose decreased in intensity, and the spot corresponding to the phthalide increased in intensity.

These results indicate that the 2-hydrogen phthaloyl derivative of dl-dihydrodideoxystreptose can be prepared, but that it is extremely unstable to weak acid. It is readily converted to the phthalide and/or other materials. Because a pure phthalate could not be obtained, this method of resolution was abandoned.

One procedure that has been used for the optical resolution of racemic diols is the preparation of the l-menthoxyacetyl derivatives. The resulting diastereoisomeric compounds can frequently be separated because they have different physical properties. Reaction of dl-dihydrodideoxystreptose (XIX) with l-menthoxyacetyl chloride in benzene, using

only a slight excess of pyridine, gave an 87.5% yield of a crystalline mixture of diastereoisomes. Satisfactory analytical data were obtained for this mixture. The melting point of the crude material was 79-85°, and the melting point of material that had been recrystallized three times was 85-86°. The optical rotation of the crude product was -63.8 ± 0.97°, and the optical rotation of material that had been recrystallized three times was -63.39 ± 0.67°. Thus, fractional crystallization failed to separate the two diastereoisomers.

The l-menthoxyacetyl derivative of authentic L-dihydrodideoxystreptose (XIII) was prepared. This sample showed $[\alpha]_D$ -56.02 ± 0.73° and had a melting point of 76-78°.

An attempt to separate the two disastereoisomeric l-menthoxyacetyl derivatives using a 200-transfer countercurrent distribution apparatus was made. The mixture had a distribution coefficient of 0.49 in the solvent mixture benzene-methanol-water (20:11:2). A plot of weight vs. fraction resulted in one symmetrical peak; the peak corresponded to 528 transfers. The optical rotations of material derived from the first, middle, and last portions of this peak were within 1.17° of each other. The material recovered from countercurrent distribution was crystallized from ethanol-water and then from methanol at -80°. This material was then hydrolyzed and gave racemic dihydrodideoxystreptose that had $[\alpha]_D$ 0.197 ± 0.59°.

Separation of the diastereoisomeric l-menthoxyacetyl derivatives was next attempted using GLC. The derivatives gave only one symmetrical peak when EGSS-X or QF-1 was used as the mobile phase. The trimethylsilyl derivatives were prepared (54); these also gave only one symmetrical peak

when SE-30 or QF-1 was used as the mobile phase. For these separation attempts the columns were operating at an efficiency of approximately 1290 theoretical plates. Primary and secondary hydroxyl groups are known (54) to react with trimethylchlorosilane and hexamethyldisilazine in pyridine within five seconds. In the above work it was noted that the l-menthoxyacetyl derivatives of dl-dihydrodideoxystreptose, which contain tertiary hydroxyl groups, as well as dibenzylphenyl carbinol, which was used as a model compound, had reaction half times of the order of two hours.

Resolution of dl-dihydrodideoxystreptose (XIX) using borneol instead of menthol was next attempted. Pure d-borneol and pure d-bornyloxyacetic acid were obtained (55) by crystallization of d-bornyl d-bornyloxyacetate. d-Bornyloxyacetic acid was converted into the corresponding acid chloride by the standard procedure. The d-bornyloxyacetyl derivatives of dl-dihydrodideoxystreptose were prepared but could not be crystallized even after chromatography over silicic acid. The infrared spectrum of the preparation was satisfactory for the expected structure. Attempted separation of these derivatives by GLC using the same columns as previously mentioned in the l-menthoxyacetyl derivatives was not successful; only one symmetrical peak was obtained.

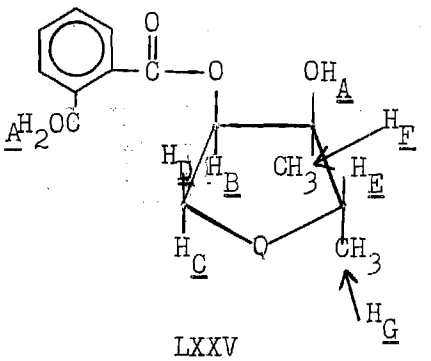
l-Menthyl hydrogen phthalate was prepared in good yield by the treatment of l-menthol with phthalic anhydride in pyridine. When l-menthyl hydrogen phthalate was treated with thionyl chloride, in an attempt to convert it to the corresponding acid chloride, phthalic anhydride was the only pure compound that could be isolated; this resulted even if the reaction was carried out at room temperature. Similarly, l-menthyl

hydrogen succinate was prepared. The acid chloride of l-menthyl hydrogen succinate could not be prepared by treating l-menthyl hydrogen succinate with thionyl chloride; the product decomposed at room temperature and gave succinic anhydride.

In spite of the discouraging results obtained in the attempted optical resolution of dl-dihydrodideoxystreptose, attempts to resolve dl-4-epidihydrodideoxystreptose (XX) were made. When dl-4-epidihydrodideoxystreptose (XX) was treated with one molar equivalent of phthalic anhydride in hot pyridine, an 81.2% yield of material was obtained that resisted crystallization. The infrared and n.m.r. spectra of this material, a tan glass, were consistent for the 2-hydrogen phthaloyl derivative of dl-4-epidihydrodideoxystreptose (LXXV). The crude material was chromatographed over silicic acid; the column fractions initially resisted crystallization. However, the fraction that contained the bulk of the material from the column crystallized after it had been refrigerated in benzene-isopropyl ether solution for about five months.

Analytical data obtained for the compound were satisfactory for the expected structure. The infrared and n.m.r. spectra of the compound were consistent for the assigned structure, and all the absorptions in the n.m.r. spectrum were able to be assigned. The assignments are given below.

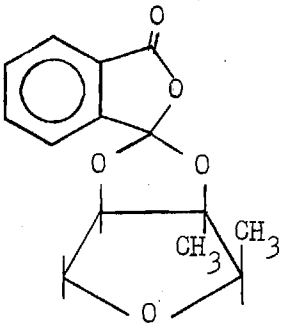
Although there was some evidence (TLC and a weak absorption in the infrared spectrum of the crude material at 5.58 μ) for the presence of a small amount of a phthalide epimeric with LXXII, no pure material corresponding to structure LXXIII could be isolated. Due to the lack of steric interaction of the two methyl groups in XIX, because they are on opposite sides of the ring, the hydroxyl groups of XIX would be expected



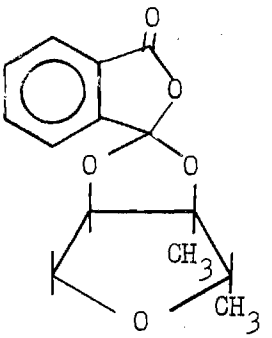
LXXV

H	τ	J, cps
Aromatic, H_A	2.07-2.75	
B	4.78	BD = 3.0
C	5.79	BC = 5.4
D	6.09	CD = -11.1
E	6.10	EG = 6.4
F	8.71	
G	8.82	

to be more nearly cis than those of XX. Steric interaction of the methyl groups of XX would be expected to pucker the ring, and the hydroxyl groups



LXXII



LXXIII

of XX would not be as nearly cis as those of XIX. Consequently, the cis fusion of two five-membered rings required for the formation of the phthalide (LXXII) would be less favorable.

l-Menthoxyacetyl and d-bornyloxyacetyl derivatives of dl-4-epidihydrodideoxystreptose were prepared. The derivatives had satisfactory infrared spectra for the expected structures, but even after chromatography over silicic acid, no crystalline material could be obtained.

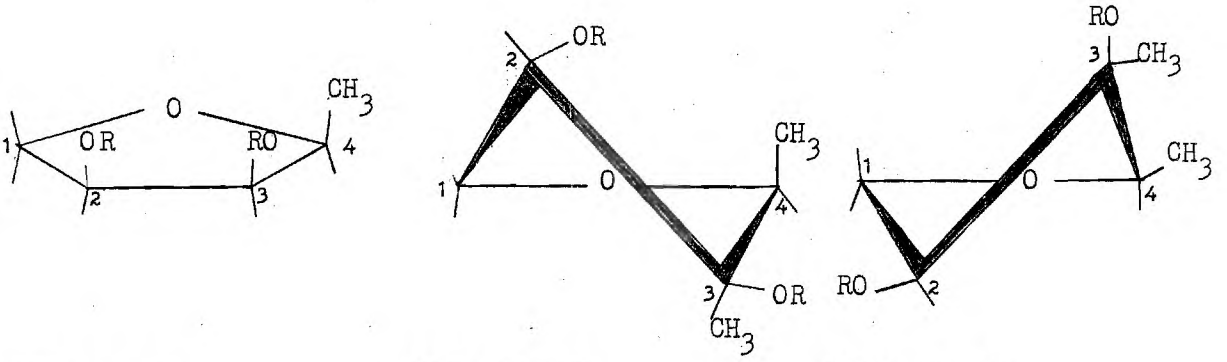
Certain of the physical data obtained for dl-dihydrodideoxystreptose and dl-epidihydrodideoxystreptose invite speculation as to the

conformations possible for the rings of these compounds and certain of their derivatives. First, the effect on ring conformation of the size of the substituent groups and the effects of hydrogen bonding that might be possible will be considered. Next, the absorption positions in the n.m.r. spectra of certain of the groups and shifts that depend on relative stereochemistries are considered. Finally, a Karplus-type relationship is derived for these tetrahydrofuran derivatives that gives internally consistent bond angles and constants for the Karplus equations.

Both dl-dihydrodideoxystreptose and dl-4-epidihydrodideoxystreptose contain cis-1,2-hydroxyl groups on the five-membered tetrahydrofuran rings. By examination of Dreiding molecular models of these compounds, the oxygen-oxygen distance between the two hydroxyl groups was determined to be 2.5 Å if the tetrahydrofuran ring is planar. The oxygen-oxygen distance increases to approximately 2.9 Å when the ring is distorted maximally. When the compounds are dissolved in inert solvents, it would be expected that hydrogen bonding between the hydroxyl groups would be a strong, but not necessarily overpowering influence on the conformation of the ring. The optimum oxygen-oxygen distance for efficient hydrogen bonding in 1,2-diols has been estimated to be 2.5-2.9 Å (91). Since this range is similar to that which is possible for these compounds, hydrogen bonding of the 1,2-diol group would not necessarily contribute strongly to buckling of the ring.

dl-Dihydrodideoxystreptose (XIX) does contain three groups on the same side of the ring, hydroxyl groups at C_2 and C_3 (throughout this discussion, the streptose numbering system is maintained for these compounds) and a methyl group at C_4. It seems reasonable that the ring could buckle

to a small extent in order to relieve these serious non-bonded interactions. If the tetrahydrofuran ring were buckled such that C_3 was below the plane of the other atoms (XIXa), the C_3 hydroxyl group would be more

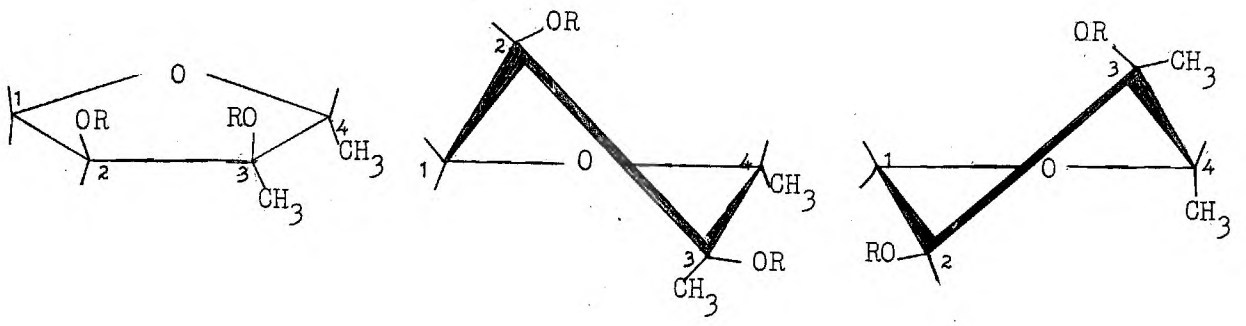


XIX, R = H XIXa, R = H XIXb, R = H

LXVII, R = p-NO_2-C_6H_4C- LXVIIa, R = p-NO_2-C_6H_4C- LXVIIb, R = p-NO_2-C_6H_4C-

remote than the C_2 hydroxyl group and the C_4 methyl group than if the ring were planar. However, this buckling brings the C_2 hydroxyl group and C_4 methyl group into closer proximity. On the other hand, if the ring were buckled so that the C_3 carbon atom was bent above the plane of the other ring atoms (XIXb), all substituent groups are farther apart than if the ring were not buckled. Qualitatively, it would seem that this conformation would be the most reasonable for dl-dihydrodideoxystreptose.

dl-4-Epidihydrodideoxystreptose (XX) contains cis-methyl groups at C_3 and C_4 of the tetrahydrofuran ring. It would seem reasonable that the tetrahydrofuran ring would buckle somewhat so that these cis-methyl groups could be as far apart as possible. Two such ring conformations are possible: one with C_3 elevated below the plane of the other atoms of the ring (XXa) and one with C_3 above the plane of the other ring atoms (XXb). Although in either conformation the methyl groups are farther apart than



XX, R = H XXa, R = H XXb, R = H

LXXIV, R = p-NO_2-C_6H_4C(=O)- LXXIVa, R = p-NO_2-C_6H_4C(=O)- LXXIVb, R = p-NO_2-C_6H_4C(=O)-

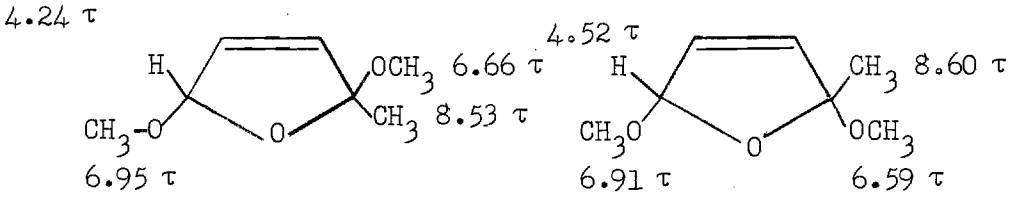
if no ring buckling were present, there is qualitatively no difference in the two ring conformations. Thus it would appear that dl-4-epidihydrodideoxystreptose could exist in either of these two conformations (XXa or XXb).

Crystalline bis-p-nitrobenzoyl derivatives were obtained for both dl-dihydrodideoxystreptose and dl-4-epidihydrodideoxystreptose. The possibility of hydrogen bonding does not exist in these compounds, and it would be expected that the ring would buckle in such a way so as to relieve the steric interactions of the substituents. An examination of molecular models reveals that in LXVII, the bis-p-nitrobenzoyl derivative of dl-dihydrodideoxystreptose, the most reasonable conformation for the ring would be with C_3 elevated above the plane of the other atoms in the ring as shown in LXVIIb. This would place the two bulky p-nitrobenzoyl groups at the farthest possible distance from each other and would eliminate the possibility of interaction of the p-nitrobenzoyl group at C_2 with the methyl group at C_4. This conformation (LXVIIb) is shown above along with LXVIIa, the alternate and less likely conformation in which

C_3 is below the plane of the other ring atoms.

In LXXIVa, the bis-p-nitrobenzoyl derivative of dl-4-epidihydrodideoxystreptose, a similar conformation LXXIVb seems most reasonable because the p-nitrobenzoyl groups, as well as the methyl groups, are farther from each other than if C_3 were below the plane of the other ring atoms as in LXXIVa. These conformations are shown above.

By consideration of the n.m.r. spectra of many of the compounds described in this research, it is possible to derive the correlation that a hydrogen or the hydrogens of a methyl group are deshielded when they are oriented cis-1,2 or cis-1,3 to the oxygen of a hydroxyl, methoxyl, or acyloxy group relative to that proton or group of protons situated trans to such groups. The 2,5-dimethoxy-2,5-dihydrofurans prepared in this work are good examples of these effects. The absorption positions of the pertinent protons of cis- and trans-2,5-dimethoxy-2,5-dihydro-2-methylfuran are shown below by their structural formulas.

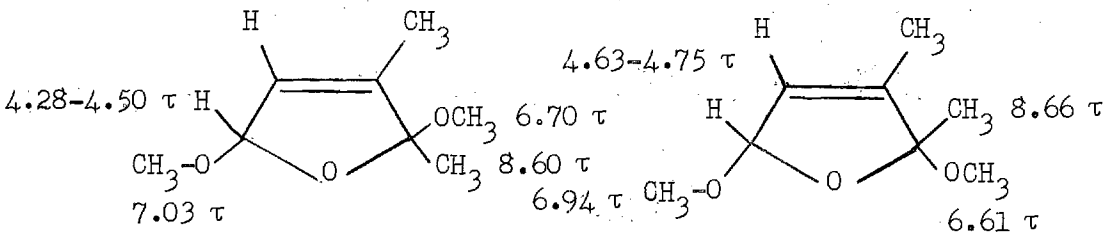


For these compounds the ring would be expected to be planar or very nearly so. It is seen that the most marked deshielding effect is on the hydrogen at position 2 (0.28 ppm) caused by the methoxy group at position 5 in the trans compound relative to the methyl group at position 5 in the cis compound. Similarly, it is seen that the methyl group at position 5

is deshielded by 0.07 ppm by the methoxyl group at position 2 in the trans compound. In the cis compound the methoxyl groups exert a mutual deshielding effect upon themselves of 0.04 and 0.07 ppm, respectively.

The magnitudes of these deshielding effects appear to be related to the distance of the particular group from the oxygen atom of the methoxyl group. Measurements using Dreiding models reveal that the hydrogen at position 2 is 3.7 Å from the oxygen atom of the methoxyl group at position 5 in the trans compound, the average position of a proton of the methyl group at position 5 is 4.1 Å from the oxygen atom of the methoxyl group at position 2 in the trans compound, and the average position of a proton of a methoxyl group is approximately 4.5 Å from the oxygen atom of the methoxyl group in the cis compound.

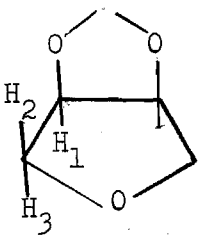
A similar type of deshielding is observed in cis- and trans-2,5-dimethoxy-2,5-dihydro-2,3-dimethylfurans, in which the distances involved in the shielding are approximately the same as the corresponding distances in the previously described 2-methylfuran derivative. The absorption positions of the pertinent protons are shown below.



It is seen that the methoxyl group at position 5 in the trans compound causes deshielding of the proton at position 2 by 0.31 ppm relative to the position of absorption of the proton at position 2 in the cis

compound. In the trans compound the methyl group at position 5 is deshielded by 0.06 ppm relative to the corresponding methyl group in the cis compound. This deshielding is caused by the methoxyl group at position 2 which is on the same side of the ring as the methyl group at position 5. The methoxyl groups in the cis compound mutually deshield each other by 0.06 and 0.09 ppm.

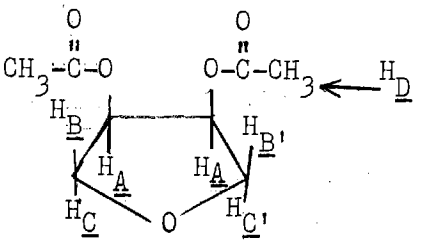
The n.m.r. absorption positions for the protons of a number of cyclic esters of meso-3,4-dihydroxytetrahydrofuran have recently been reported (93). These data are summarized below.



Compound	τ_1	τ_2	τ_3	$\Delta(2,3)$ ppm.	J, gem
Phosphate	4.60	5.53	6.03	0.50	-11
Borate	5.10	5.95	6.53	0.58	- 9.5
Sulfite	4.44	5.85	6.35	0.50	-11
Carbonate	4.77	5.80	6.42	0.62	-11.4 $\pm$ 0.2
Dimethylketal	5.30	6.15	6.70	0.55	-10.0

Because all of these compounds contain two five-membered rings having a cis fusion, it would be expected that the H_2-H_1 dihedral angle would be nearly 120°, and that the dihedral angle of H_2 and the oxygen at position 2 would be nearly 0°. Thus it would be anticipated that the deshielding effect on H_2 by the anisotropy of the C_3 carbon oxygen bond would be maximum. The difference in absorptions of H_2 and H_3 are seen to range from 0.50 to 0.62 ppm.

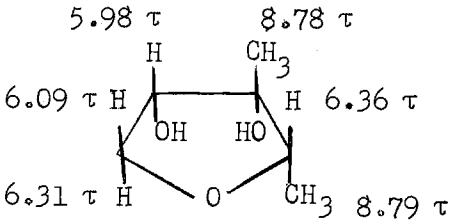
An analysis of the n.m.r. spectrum of the diacetate of meso-3,4-dihydroxytetrahydrofuran has also recently been reported (94). These data are given below. Again, it is seen that the hydrogen at position 2 cis



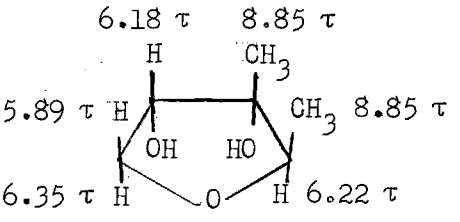
H	τ	J, cps
A	4.60	AA' = 5.4 ± 0.2
B	5.53	AB = 5.6 ± 0.1
C	5.95	AC = 4.2 ± 0.1
D	7.94	BC = -9.6 ± 0.1

to the acetoxy group is deshielded by 0.42 ppm.

When this same correlation is attempted using the n.m.r. spectra of dl-dihydrodideoxystreptose, dl-4-epidihydrodideoxystreptose, and certain derivatives of these compounds, it is found that the simple explanation outlined above does not account by itself for all of the observations. The n.m.r. absorptions of dl-dihydrodideoxystreptose and dl-4-epidihydrodideoxystreptose are given by their formulas below.



XIX

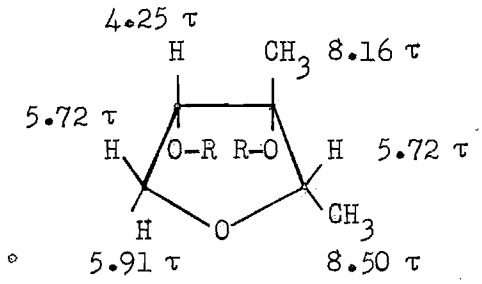


XX

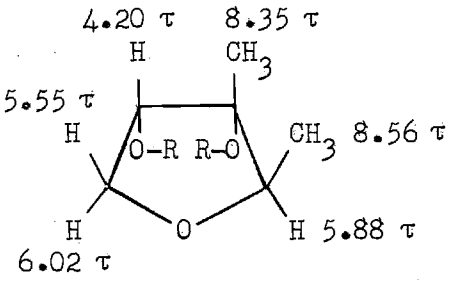
It is seen that the hydrogen at C_4 (streptose numbering) of XX is deshielded by 0.14 ppm when compared with the corresponding hydrogen in XIX, and the methyl group at C_4 of XIX is deshielded by 0.06 ppm when compared with the corresponding group of XX. These observations are in accord with the simple explanation outlined above, that is, deshielding by the anisotropy of the C_3 carbon oxygen bond. This simple explanation cannot be used to explain the absorptions observed for the protons on carbons

1 and 2. It is seen that the proton on C_1 that is trans to the hydroxyl group on C_2 absorbs 0.23 ppm to lower field than the proton on C_1 cis to the hydroxyl group at C_2 for XIX, and 0.46 ppm to lower field for XX. In addition, the absorption positions for the hydrogens at C_2 are not very similar for the two compounds. It may be, that because of the particular ring conformations for the two compounds, the anisotropies of the various single bonds result in a deshielding of the hydrogen on C_2 in XIX and the hydrogen trans to the hydroxyl group at C_1 in XX. This explanation is speculative.

The n.m.r. absorptions of the pertinent protons for the crystalline bis-p-nitrobenzoyl derivatives of dl-dihydrodideoxystreptose (LXVII) and dl-4-epidihydrodideoxystreptose (LXXIV) are shown by the formulas below.



LXVII



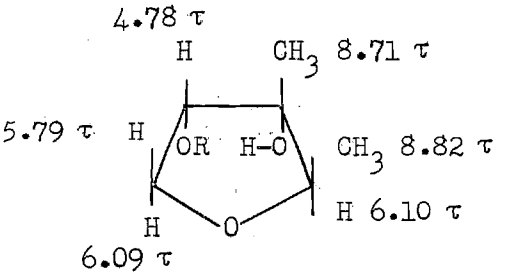
LXXIV

$R = p\text{-}NO_2\text{-}C_6H_4C(=O)-$

Again, the protons at C_1 that are cis to the oxygen at C_2 appear to be shielded (0.19 ppm for LXVII and 0.47 ppm for LXXIV) compared to position of absorption of the proton at C_1 that is trans to the oxygen function at C_2. From an examination of Dreiding molecular models of these compounds, it would appear that the very large p-nitrobenzoyloxy groups

present in these derivatives would be as far apart as possible. If this were the case, the diamagnetic anisotropic effect of the carbonyl group would result in an enhanced shielding of that hydrogen at C_1 that is cis to the oxygen function at C_2.

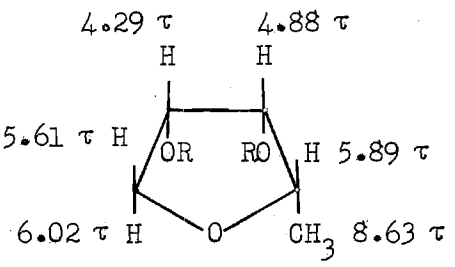
The absorption positions for the pertinent protons of the crystalline 2-hydrogen phthaloyl derivative of dl-4-epidihydrodideoxystreptose are shown below by the formula. Again, that hydrogen at C_1 that is



LXXV R = o-HO_2C-C_6H_4-$\overset{O}{\overset{\|}{C}}$-

cis to the oxygen function at C_2 appears to be shielded relative to that hydrogen at C_1 trans to the oxygen function at C_2. An explanation similar to that cited above may explain this difference in shielding.

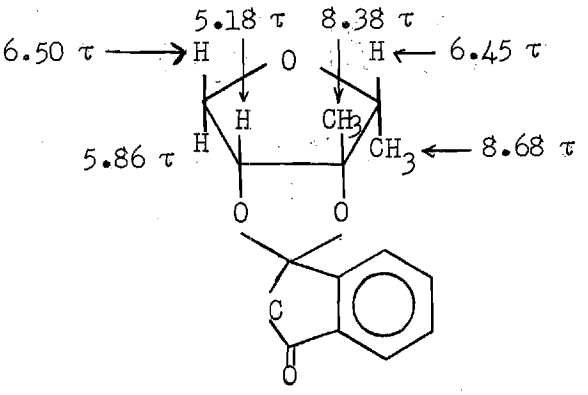
Another case similar to the ones just described is that of the bis-hydrogen phthaloyl derivative of dl-3-nordihydrodideoxystreptose (XXXIIIa). The positions of absorption of the pertinent protons are described below.



XXXIIIa R = o-HO_2C-C_6H_4-$\overset{O}{\overset{\|}{C}}$-

The proton at C_1 that is cis to the oxygen function at C_2 is shielded by 0.41 ppm relative to the proton at C_1 that is trans to the oxygen function at C_2. The explanation proposed for this shielding is the same as that previously described for the same type of shielding observed in LXVII, LXXIV, and LXXV.

During an attempted preparation of the hydrogen phthalate derivative of dl-dihydrodideoxystreptose (XIX), a crystalline side reaction product was obtained. The phthalide structure LXXII has been assigned to this compound. The pertinent n.m.r. absorptions of this compound are given below beside the structural formula. In this compound, it is seen



LXXII

that the hydrogen at C_1 that is cis to the oxygen function at C_2 is deshielded by 0.64 ppm relative to the hydrogen at C_1 that is trans to the oxygen function at C_2. This then is another example of the correlation previously mentioned. That this example conforms with the previously mentioned examples, in contrast to the hydrogen phthaloyl and bis-p-nitrobenzoyl derivatives just mentioned, is probably a result of the fact that

that this compound contains two cis fused five-membered rings and no carbonyl group near the geminal protons. The positions of absorptions of the two geminal protons (Δ = 0.64 ppm) is in quite good agreement with the data previously described for the cyclic esters of meso-3,4-dihydroxytetrahydrofuran.

Thus, it would appear that the correlations discussed above are valid where rigid conformations of the tetrahydrofuran rings are present or where groups that may contribute to a diamagnetic anisotropic effect are not present in the tetrahydrofuran ring.

In 1959 Karplus (94) proposed an equation, derived from theoretical considerations, which related the proton coupling constants in CH-CH fragments to the dihederal angle, ϕ, between the relevant C-H bonds.

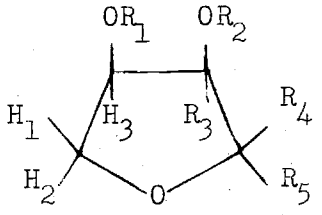
$$J = k_1 \cos^2\phi - c \qquad 0^\circ \leqslant \phi \leqslant 90^\circ$$

$$J = k_2 \cos^2(120 \pm \phi) - c \qquad 90^\circ \leqslant \phi \leqslant 180^\circ$$

It was hoped that it would be possible, from the coupling constants observed for the C_1-C_2 CH_2-$\dot{C}H$- fragments in dl-dihydrodideoxystreptose (XIX), dl-4-epidihydrodideoxystreptose (XX), and certain derivatives of these compounds, to derive the dihederal angles for these interactions.

The positions of absorption of the various protons and the coupling constants (given in cps) for dl-dihydrodideoxystreptose (XIX), dl-4-epidihydrodideoxystreptose (XX), and certain derivatives and related compounds are given in Table 1. The spectral analyses given in Table 1 have been matched with computed spectra (84).

Table 1. Summary of Calculated N.M.R. Spectral Data.



COMPOUND

	R_1	R_2	R_3	R_4	R_5	H_1	H_2	H_3	R_3	R_4	R_5	1,2*	1,3	2,3	3,4	4,5
XIX	H	H	CH_3	CH_3	H	6.09	6.34	5.98	8.78	8.79	6.36	- 8.75	4.90	7.00	---	---
LXVIII	NB[1]	NB[1]	CH_3	CH_3	H	5.91	5.72	4.25	8.16	8.50	5.72	-11.1	2.9	4.9	---	---
LXXVI	P[2]	P[2]	CH_3	CH_3	H	5.86	6.50	5.18	8.38	8.68	6.45	-11.3	0	3.2	---	---
XX	H	H	CH_3	H	CH_3	5.89	6.35	6.18	8.85	6.22	8.85	-10.00	3.25	5.25	---	---
LXXIV	NB[1]	NB[1]	CH_3	H	CH_3	6.02	5.55	4.20	8.35	5.61	8.56	-11.5	2.2	5.1	---	---
LXXV	PH[3]	H	CH_3	H	CH_3	6.09	5.79	4.28	8.71	6.10	8.82	-11.1	3.00	5.4	---	---
LXXIV	PH[3]	PH[3]	H	CH_3	H	6.02	5.61	4.29	4.88	8.63	5.89	-10.2	3.9	5.5	5.6	7.4

* This coupling constant was shown to have a different size than $J_{1,3}$ and $J_{2,3}$ for compound XIX and XX by spin perturbation experiments. The author thanks Mr. Allan Douglas for these experiments.

1. NB = p-Nitrobenzoyl
2. P = Phthalidoyl
3. PH = Hydrogen phthaloyl

The original equations derived by Karplus, using a valence-bond approach, were derived for substituted ethanes assuming free rotation about the carbon-carbon bond. The effects of the electronegativity of various substituents, hybridization at carbon, and different carbon-carbon bond lengths were neglected. Using these approximations, the values obtained for k_1, k_2, and c were 8.5, 9.5, and 0.28, respectively. Because free rotation about the C_1-C_2 bond is impossible in the cyclic compounds being considered, and the effective electronegativities of the substituent groups are different, the original Karplus relationship would not be expected to be applicable to these systems, although a Karplus-type relationship using different values of k_1, k_2, and c should be applicable.

Bothner-By and Glick (101) have shown that vicinal coupling constants in a given series of structurally similar compounds are functions of the Huggins electronegativity of the substituent groups, and they have obtained equations relating the magnitude of the vicinal coupling constants to the Huggins electronegativity of the particular substituent atom for a series of ethyl and isopropyl derivatives.

$$J_{HH'} = 8.4 - 0.14\ E \quad \text{ethyl derivative}$$

$$J_{HH'} = 8.4 - 0.55\ E \quad \text{isopropyl derivative}$$

$$E = \text{Huggins electronegativity of the substituent group}$$

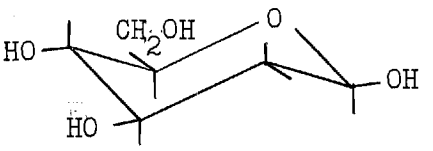
Lenz and Heeschen (102) have determined the dihederal angles and conformations for a number of carbohydrates by assuming that the original Karplus equations would give the proper relationship of $J_{HH'}$ to ϕ, for the carbohydrates studied, if modified by a proportionality constant, F. The proportionality constant, F, alters the magnitude but not the form of the

angular dependence of Ø on J. The original Karplus equations, modified by the proportionality constant, F, that were used by Lenz and Heeschen are given below. The value of F was determined by solving the two equations simultaneously after analysis of the n.m.r. spectrum of β-2-deoxyglucopyranose for the required coupling constants.

$$J^{\beta}_{H_1H_2\ eq} = F\ [8.5\ \cos^2\phi\ -0.28]$$

$$J^{\beta}_{H_1H_2\ ax} = F\ [9.5\ \cos^2(\phi + 120^\circ)\ -0.28]$$

It was also assumed that the average projected angle of the carbon-hydrogen bonds at C_2 was 120°. If, in the β-anomer of 2-deoxyglucopyranose shown below, the dihedral angle between the axial C_1H bond and the equitorial C_2H bond is Ø, then the dihedral angle between the axial C_1H bond and the axial C_2H bond is Ø + 120°.



The Karplus equations modified by the proportionality constant, F, determined to be 1.09 ± 0.05 determined as described above, are given below.

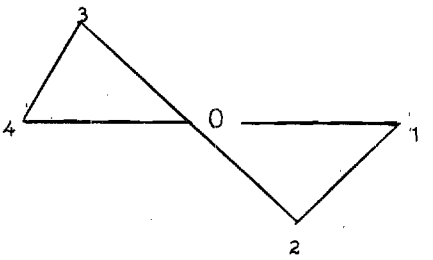
$$J^{\beta}_{H_1H_2\ eq} = 9.26\ \cos^2\phi\ -0.31$$

$$J^{\beta}_{H_1H_2\ ax} = 10.36\ \cos^2(\phi + 120^\circ)\ -0.31$$

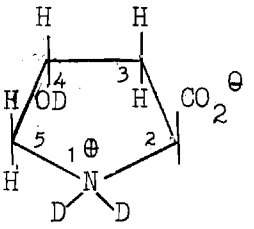
Abraham et al. (103) have employed a set of Karplus-type equations similar to those used by Lenz and Heeschen to determine the conformation of thirteen derivatives of 1,2-O-isopropylidine-α-D-xylohexofuranose. In the equations used by Abraham et al., which are given below, only the angular dependent term in the original Karplus equations was multiplied by the factor 1.09 that was determined by Lenz and Heeschen. Complete

$$J = 9.27 \cos^2\phi - 0.28 \quad 0 \leqslant \phi \leqslant 90^\circ$$
$$J = 10.36 \cos^2\phi - 0.28 \quad 90 \leqslant \phi \leqslant 180^\circ$$

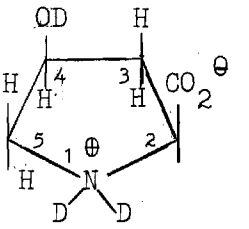
analyses of the n.m.r. spectra of the thirteen derivatives of 1,2-O-isopropylidine-α-D-xylohexofuranose were obtained, and it was shown that without exception the furanose ring in all the compounds studied exists in the "skew conformation" in solution. The "skew conformation" for the furanose ring is shown below.



Abraham and McLauchlan (104,105) have obtained complete analysis of the n.m.r. spectra of trans-hydroxy-L-proline and allo-hydroxy-L-proline. Using the observed vicinal coupling constants between the relevant C-H bonds, these workers have experimentally obtained a set of Karplus-type



trans-Hydroxy-L-proline



allo-Hydroxy-L-proline

equations that gave internally consistent bond angles for the two epimers. The equations used for the C_4-C_5 fragment are given below. The solution

$$4.09 = k \cos^2\phi_1 - c$$
$$1.22 = k \cos^2(120 \pm \phi_1) - c$$
$$0.94 = k \cos^2\phi_2 - c$$
$$4.57 = k \cos^2(120 \pm \phi_2) - c$$

of these equations gives k = 10.1 cps., c = 0, $\phi_1 = 50.4^\circ$ and $\phi_2 = 72.25^\circ$. The bond angles for the C_{2-3} and C_{3-4} fragments were obtained similarly, and all the bond angles obtained for the particular compound were consistent for a single conformation.

Because of the success of this method in obtaining bond angles from vicinal coupling constants, and the similarity between the C_{4-5} fragment of the two epimeric proline derivatives and the epimeric diols XIX and XX, this method was applied to the problem of calculating bond angles in XIX, XX, and their bis-p-nitrobenzoate derivatives. Using the vicinal coupling constants obtained from the computed spectra of dl-dihydrodideoxystreptose (XIX) and (XX), four Karplus-type equations in four unknowns are obtained. The four equations were solved (106) using a Burroughs B-5500 computer and gave values of 4.14 and -3.03 for k and c, respectively.

$$\text{XIX} \quad \begin{cases} 4.90 = k \cos^2\phi_1 - c \\ 7.00 = k \cos^2(\phi_1 \pm 120) - c \end{cases}$$

$$\text{XX} \quad \begin{cases} 3.25 = k \cos^2\phi_2 - c \\ 5.25 = k \cos^2(\phi_2 \pm 120) - c \end{cases}$$

Reversing the values of 4.90 and 7.00 in the first two equations of the set and solving the resulting set of four equations gave the same values for k and c. This result was also obtained when the values of the coupling constants observed for XX were reversed and the equations solved.

From the Karplus-type equation that results from the above constants, which is shown below, for dl-dihydrodideoxystreptose (XIX) and dl-4-epidihydrodideoxystreptose (XX), two possible values of ϕ are obtained for each coupling constant.

$$J = 4.14 \cos^2\phi + 3.03$$

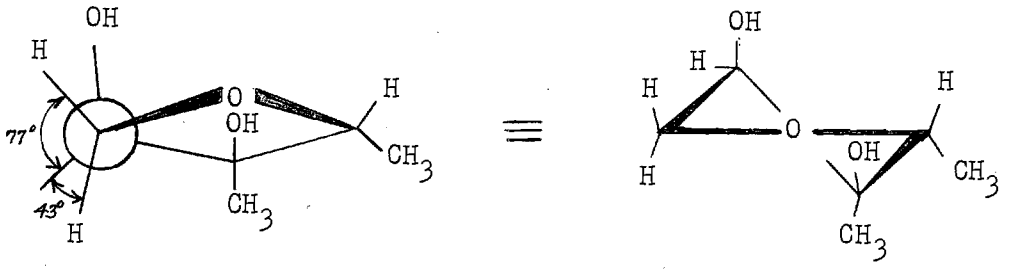
dl-Dihydrodideoxystreptose (XIX)		dl-4-Epidihydrodideoxystreptose (XX)	
J	ϕ	J	ϕ
7.00	12° or 168°	5.25	43° or 137°
4.90	48° or 132°	3.25	77° or 103°

For the bond angles between the two geminal protons at C_1 and the proton at C_2 there are four possibilities for each of the two compounds.

For XX, (2) and (3) are excluded as possibilities because the molecule cannot maintain a projected angle of 120° between the geminal protons and have these bond angles. The two remaining possibilities for the bond angles in question for XX are (1) and (4). Possibility (4) is excluded

For XIX	For XX
(1) 12° and 48°	(1) 43° and 77°
(2) 12° and 132°	(2) 43° and 103°
(3) 48° and 168°	(3) 77° and 137°
(4) 132° and 168°	(4) 103° and 137°

because of the strain that would be involved if the molecule would adopt these bond angles. The molecule must therefore have the bond angles in (1). The estimated conformation of XX in 7% deuteriochloroform solution is shown below. It is seen that C_2 must be above and C_3 below the plane

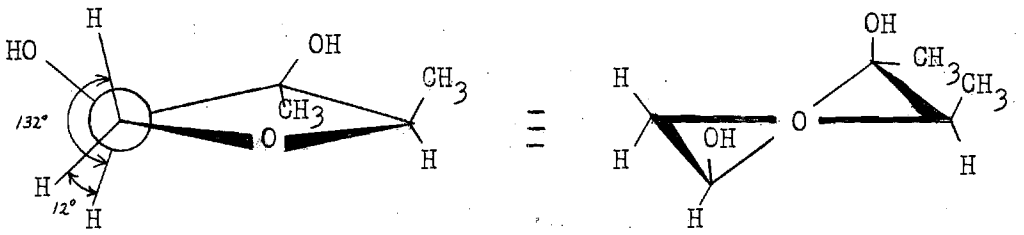


XX

of the other ring atoms when the bond angles are 43° and 77° in the C_{1-2} fragment. The experimental error is probably ± 5° at the most for the bond angles quoted.

The bond angles in question for XIX can be obtained in a similar manner. Possibilities (1) and (4) for the bond angles of XIX are excluded because the projected angles between the geminal protons must be 120°. Bond angles given in (3) are unlikely because of the amount of strain in the molecule if it were in the conformation dictated by these bond angles.

The bond angles of 12° and 132° are therefore the only reasonable ones for the vicinal protons. The conformation of XIX in 7% deuteriochloroform is shown below.



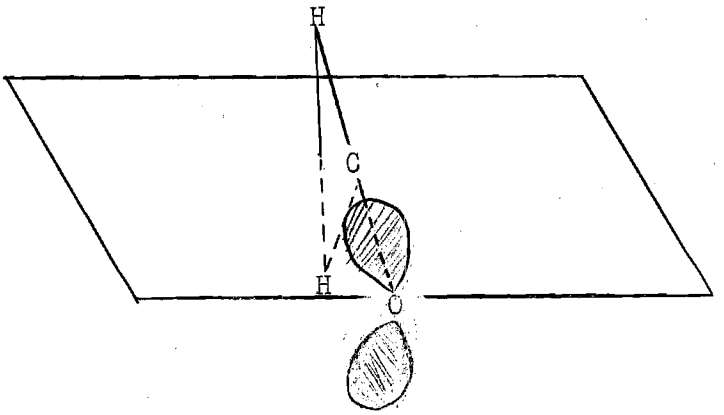
XIX

This conformation is in agreement with the qualitative prediction made earlier on the assumption that the ring would buckle in such a way so as to relieve the steric interaction of the two hydroxyl groups and the methyl group that are on the same side of the ring.

Because the Karplus equations predict that k_1 and k_2 are different if $\phi_2 \geqslant 90^\circ$, an attempt was made to obtain different values of k for the Karplus equation for XIX and XX by assignment of the coefficient k in the first three original equations as k_1 and the coefficient in the last equation as k_2. The solution of the four equations using the previously obtained value of c of -3.03 gave $k_1 = k_2 = 4.14$, which is the same value obtained for k in the solution of the original set of equations.

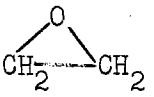
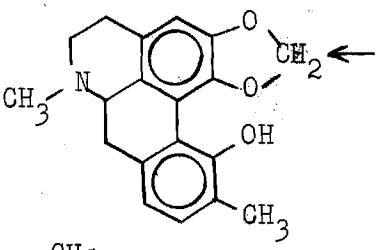
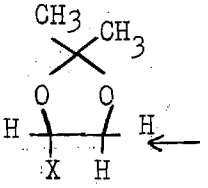
Pople and Bothner-By (107) have shown from theoretical considerations in systems of the type R-CH_2-O-R that the more nearly perpendicular the line joining the geminal protons is to the nodal plane of the orbitals of the unshared electrons on oxygen, the more positive the geminal

coupling constant. That is, the more nearly the geminal protons eclipse the orbitals of the unshared electrons on oxygen the more positive the geminal coupling constant.



Maximum positive value J_{gem}

Selected examples are given below.

Compound	J_{gem}
	+ 5.5
	± 1.5
 X = halogen	- 8.3

Inspection of molecular models reveals that if XIX had bond angles of 48° and 168° the extent of eclipsing of the orbitals of the unshared electrons on oxygen by the geminal protons would be very nearly the same as that in XX, which has bond angles of 43° and 77° and a geminal coupling constant of -10.00. If the bond angles in question for XIX were 48° and 168° the geminal coupling constant would be expected to be near -10.00. However, if the bond angles, in question for XIX were 12° and 132° a more positive (less negative) geminal coupling constant would be expected because inspection of molecular models reveals that the orbitals of the unshared electrons on oxygen are significantly more eclipsed by the geminal protons than when the bond angles are 48° and 168°.

Because the geminal coupling constant for XIX (-8.75) is more positive by 1.25 than is the geminal coupling constant for XX (-10.00), and because the conformation for XIX dictated by bond angles of 48° and 168° is much more strained than the conformation that has bond angles of 12° and 132°, it is concluded that the bond angles of XIX in question are 12° and 132°.

As previously mentioned, the proton on C_1 that is <u>trans</u> to the hydroxyl group on C_2 absorbs at 0.23 ppm to lower field than the proton on C_1 <u>cis</u> to the hydroxyl group at C_2 for XIX, and 0.46 ppm to lower field for XX. This is easily explained after consideration of the conformational drawings of XIX and XX. In XIX the hydroxyl group at C_2 is between the two geminal protons at C_1 and the effect on the chemical shifts of the geminal protons would be expected to be more nearly the same (0.23 ppm different), as observed, than in XX, where the hydroxyl group is not between the two geminal protons (0.46 ppm different), and the shielding

of the two protons would be expected to be more different.

Using the coupling constants obtained for the bis-p-nitrobenzoates of XIX (LXVII) and XX (LXXIV) the four Karplus-type equations shown below were obtained.

$$\text{LXVII} \quad \begin{cases} 2.9 = k \cos^2 \phi_1 - c \\ 4.9 = k \cos^2 (120 \pm \phi_1) - c \end{cases}$$

$$\text{LXXIV} \quad \begin{cases} 2.2 = k \cos^2 \phi_2 - c \\ 5.1 = k \cos^2 (120 \pm \phi_2) - c \end{cases}$$

These equations were solved simultaneously and resulted in two solutions $k = 5.36$, $c = 0$; and $k = 4.70$ and $c = -0.54$. For the derived equation for the first solution, $J = 5.36 \cos^2 \phi$, the following possible angles for each coupling constant were obtained.

	J	ϕ
LXVII	2.9	42° or 138°
	4.9	22° or 158°
LXXIV	2.2	51° or 129°
	5.1	12° or 168°

The possibilities for the bond angles in question for the two compounds are therefore:

LXVII		LXXIV	
(1)	42° and 22°	(1)	57° and 12°
(2)	42° and 158°	(2)	57° and 168°
(3)	22° and 138°	(3)	12° and 129°
(4)	138° and 158°	(4)	129° and 168°

For the other possible solution, $J = 4.70 \cos^2 \phi + 0.54$, the following corresponding values were obtained for the possible angles for each coupling constant. These values are shown below.

	J	ϕ
LXVII	2.9	45° or 135°
	4.9	16° or 164°
LXXIV	2.2	53° or 127°
	5.1	10° or 170°

Also the possibilities for the bond angles in question in the two compounds were obtained and are also shown below.

	LXVII	LXXIV
(1)	45° and 16°	53° and 10°
(2)	45° and 164°	53° and 170°
(3)	16° and 135°	10° and 127°
(4)	135° and 164°	127° and 170°

The possible bond angles (1) and (4) from both solutions for both compounds are excluded because the projected angle of the geminal protons cannot be 120° if these are the bond angles.

If the maximum experimental error for these derived bond angles is $\pm$ 3°, it is seen from the following summary of values that both solutions give values for the bond angles for possibilities (1) and (2) that are within experimental error.

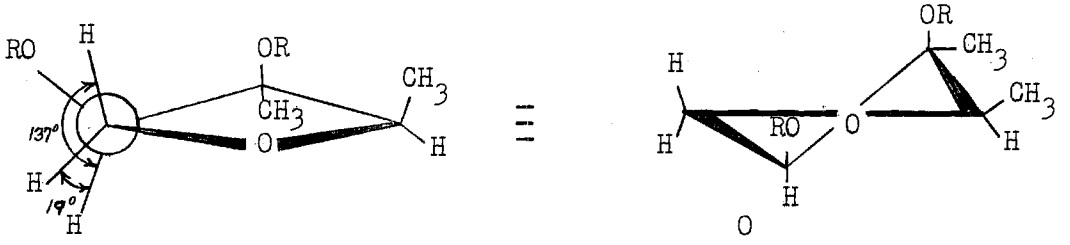
		LXVII	LXXIV
Solution 1	(2)	42° and 158°	57° and 168°
	(3)	22° and 138°	12° and 129°
Solution 2	(2)	45° and 164°	53° and 170°
	(3)	16° and 135°	10° and 127°

Averaging the corresponding values for both solutions gives:

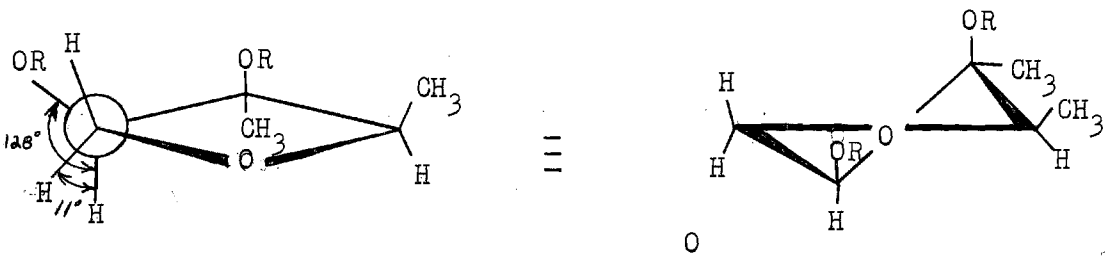
	LXVII	LXXIV
(2)	44° and 161°	55° and 169°
(3)	19° and 137°	11° and 128°

Possibility (2) for the bond angles of LXVII and LXXIV seems unlikely because of the large amount of strain present in the molecule if the molecule has these bond angles. Possibility (3) for LXVII and LXXIV seems much more likely because the molecules would be much less strained. This conclusion is in agreement with the simple qualitative prediction made earlier that assumed the ring would buckle so as to relieve steric interaction of the bulky substituent groups.

The estimated conformation for LXVII and LXXIV are shown below. The solutions obtained for the four equations in four unknowns for LXXIV and LXVII were not exact but were very nearly so. However, the solution obtained for the equations for the diols, XIX and XX, was exact.



LXVII, R = p-NO_2-C_6H_4-C(=O)-



LXXIV, R = p-NO_2-C_6H_4C(=O)-

The conformations derived for these compounds are in agreement with the simple qualitative prediction previously made after examination of molecular models. This prediction was based on the assumption that the ring would pucker so as to place the C_3 carbon atom above the plane of the ring, thereby placing the bulky p-nitrobenzoyloxy groups at the farthest possible distance from each other. In this conformation, interaction of the large p-nitrobenzoyloxy group with the substituent group at C_4 is relieved that would otherwise take place if the ring were puckered in the opposite way with C_3 below the plane of the other atoms of the ring.

It is also seen that the ring is puckered to a slightly greater extent in LXVII than in LXXIV. This is reasonable and is easily explained by the fact that the 1,3-steric interaction of the C_2 and C_4 substituent groups of LXVII involve a p-nitrobenzoyloxy group and a methyl group and would be expected to be more severe and consequently result in more distortion of the ring than the steric interaction of a p-nitrobenzoyloxy group and a hydrogen atom as is the case in LXXIV.

Although the four carbon atoms of the tetrahydrofuran ring are held in a rigid position in the phthalide (LXXII) because of the cis fusion of the two five-membered rings, the average position of the oxygen atom of the tetrahydrofuran ring is probably on the opposite side of the ring from

the oxygen atoms at C_2 and C_3. This probably results from electrostatic repulsion of the oxygen atom in the tetrahydrofuran ring with the oxygen atoms at C_2 and C_3. The eclipsing of the geminal protons by the nonbonding orbitals on oxygen would therefore not be near a maximum. Consequently, a geminal coupling constant more positive than the observed value of -11.3 would be anticipated if this were the only factor affecting the magnitude of J_{gem}. Pople and Bothner-By (107) have shown from theoretical considerations that an electronegative atom situated β to a methylene group causes a large negative shift in the value of J_{gem}.

Examination of molecular models of the phthalide (LXXII) reveal that the geminal protons are nearly maximally eclipsed by the nonbonding orbitals of the oxygen atom at C_2 (situated β to the geminal protons). These nonbonding orbitals are also held in a rigid position by the cis ring fusion. The relatively large negative value of J_{gem} in the phthalide can be explained by these observations.

As previously mentioned, the geminal coupling constants for a number of cyclic esters of meso-3,4-dihydroxytetrahydrofuran range from -9.5 to -11.4 ± 0.2 cps (see page 179). As in the case of the phthalide, the oxygen atoms at C_2 and C_3 in these molecules are held in a rigid position by the cis ring fusion. Consequently, the geminal protons are nearly maximally eclipsed by the nonbonding orbitals of the β oxygen atom. In these compounds a relatively large negative value of J_{gem} would be expected, as observed.

In the diols, XIX and XX, the extent of eclipsing of the geminal protons by the nonbonding orbitals of the oxygen atoms of the C_2 hydroxyl group is reduced by hydrogen bonding of the two cis hydroxyl groups.

Also, there is no cis ring fusion to insure a rigid position of the oxygen at C_2 as in the case of the phthalide. The less negative values of J_{gem} of XIX (-8.75) and XX (-10.00) relative to the phthalide (-11.3) (LXXII) is qualitatively explained by these facts.

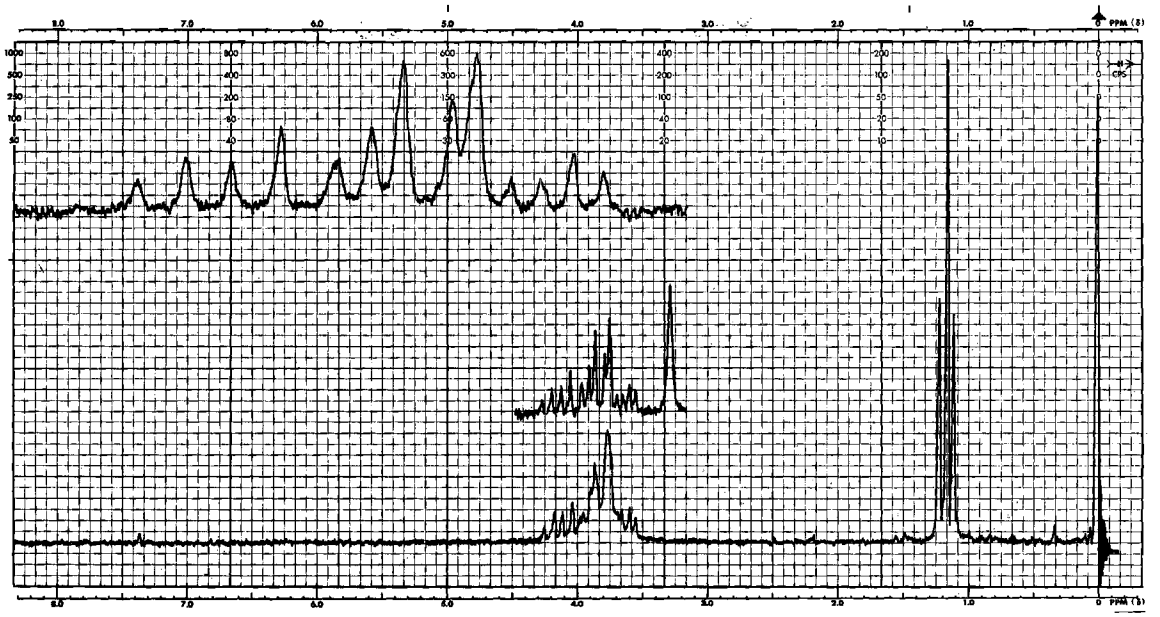


Figure 2. The Nuclear Magnetic Resonance Spectrum of dl-4-Epi-dihydrodideoxystreptose.

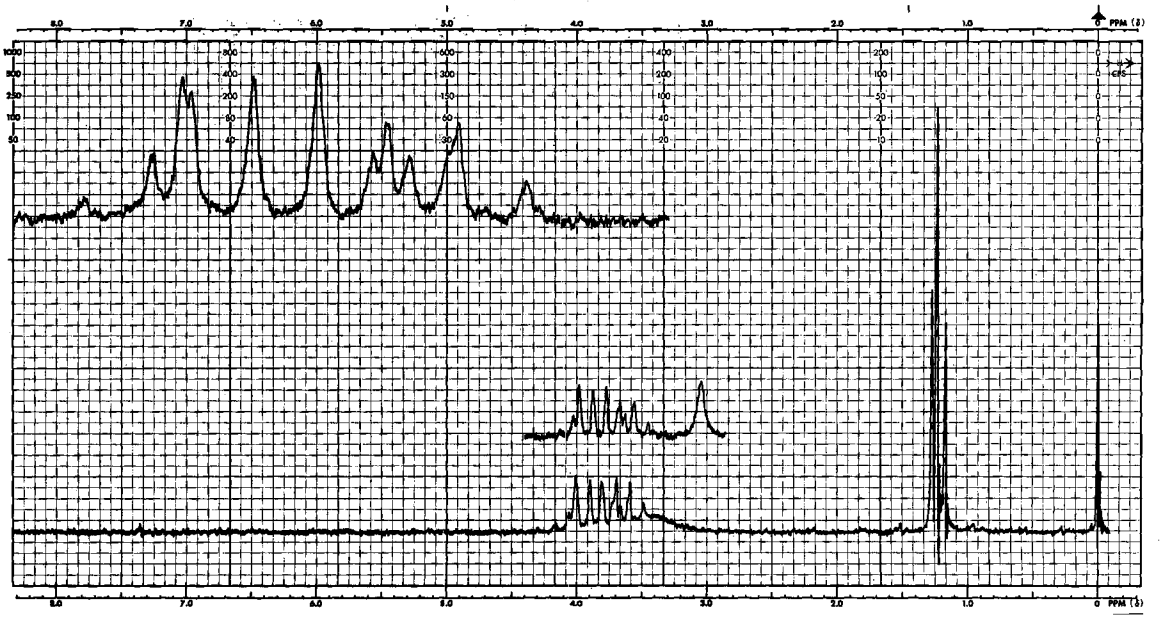


Figure 3. The Nuclear Magnetic Resonance Spectrum of dl-Dihydro-dideoxystreptose.

LITERATURE CITED*

(1) S. A. Waksman, E. Bugie, and A. Schatz, Proc. Soc. Exptl. Biol. Med., 55, 66 (1944).

(2) R. U. Lemieux and M. L. Wolfrom, Advances in Carbohydrate Chem., 3, 357-384 (1948), and references cited therein.

(3) S. A. Waksman, "The Actenomycetes," The Williams and Wilkins Co., Baltimore, Md., Vol. 1, 1959, pp. 233-236.

(4) S. A. Waksman and A. Schatz, J. Am. Pharm. Assoc., 34, 273 (1945).

(5) J. Fried and O. Wintersteiner, J. Am. Chem. Soc., 69, 79 (1947).

(6) S. Tatsuoka, T. Kusaka, A. Miyake, M. Inove, H. Hitomi, Y. Shiraishi, H. Iwasaki, and M. Imanishi, Pharm. Bull., 5, 343 (1957).

(7) N. G. Brink, F. A. Kuehl, Jr., and K. Folkers, Science, 102, 506 (1945).

(8) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, J. Am. Chem. Soc., 68, 2557 (1946).

(9) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell, and W. A. Strong, J. Biol. Chem., 160, 337 (1945).

(10) I. R. Hooper, L. H. Klemm, W. J. Polglase, and M. L. Wolfrom, J. Am. Chem. Soc., 68, 2120 (1946).

(11) H. G. Fletcher, Jr., Advances in Carbohydrate Chem., 3, 60 (1948).

(12) O. Wintersteiner and A. Klingsberg, J. Am. Chem. Soc., 73, 2917 (1951).

(13) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, ibid., 72, 1724 (1950).

(14) J. R. Dyer and A. W. Todd, ibid., 85, 3896 (1963).

(15) J. Fried, D. E. Walz, and O. Wintersteiner, ibid., 68, 2746 (1946).

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* For the complete titles of all journals referred to see Chemical Abstracts, 50, 1 J (1956).

(16) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, and K. Folkers, ibid., 69, 1234 (1947); 70, 2325 (1948).

(17) F. A. Kuehl, Jr., E. H. Flynn, F. W. Holley, R. Mozingo, and K. Folkers, ibid., 68, 536 (1946); 69, 3032 (1947).

(18) F. A. Kuehl, Jr., E. H. Flynn, N. G. Brink, and K. Folkers, ibid., 68, 2096 (1946).

(19) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, ibid., 70, 2085 (1948).

(20) F. A. Kuehl, Jr., E. H. Flynn, N. G. Brink, and K. Folkers, ibid., 68, 2679 (1946).

(21) F. A. Kuehl, Jr., R. L. Clark, M. N. Bishop, E. H. Flynn, and K. Folkers, ibid., 71, 1445 (1949).

(22) M. L. Wolfrom and C. W. DeWalt, ibid., 70, 3148 (1948).

(23) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, ibid., 68, 2405 (1946).

(24) J. Boeseken, Advances in Carbohydrate Chem., 4, 189 (1949).

(25) J. R. Dyer, W. E. McGonigal, and K. C. Rice, J. Am. Chem. Soc., 87, 654 (1965).

(26) F. Kohlransch and L. Holborn, "Das Leitvermogen der Elektrolyte," B. G. Teubner, Leipzig (1916).

(27) J. R. Dyer, private communication.

(28) M. L. Wolfrom, M. J. Cron, C. W. DeWalt, and R. M. Husband, J. Am. Chem. Soc., 76, 3675 (1954).

(29) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1942, Vol. II, p. 242.

(30) Yu. K. Yur'ev, I. K. Korobitsyna, and E. K. Brige, Zhur. Obshchei Khim., 20, 744-8 (1950). [C. A., 44, 7822e (1950).]

(31) N. O. Brace, J. Am. Chem. Soc., 77, 4157 (1955).

(32) N. A. Milas and S. Sussman, ibid., 58, 1302 (1936).

(33) C. O. Edmons, U. S. Patent 2,572,566, Oct. 23, 1951.

(34) L. Birkofeu and R. Dutz, Ann., 657, 94 (1962).

(35) N. Clauson-Kaas and F. Limborg, Acta. Chem. Scand. 1, 619 (1947).

(36) M. Gouge, Ann. Chim., 6, 648 (1957).

(37) B. Helferech, Ber. 52, 1123 (1919).

(38) L. W. Burnette, Iowa State Coll. J. Sci., 19, 9 (1944).

(39) E. E. Royals and K. C. Brannock, J. Am. Chem. Soc., 76, 1180 (1954).

(40) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964, p. 253.

(41) O. Keun-Houo, Ann. Chim., 13, 175 (1940).

(42) Page 47, this thesis.

(43) Page 45, this thesis.

(44) A. W. Ingersoll, Organic Reactions, 2, 399 (1949).

(45) H. E. Winberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, J. Am. Chem. Soc., 82, 1428 (1960).

(46) A. L. Mndzhoian ed., Syntheses of Heterocyclic Compounds, Vol. 2, p. 26, Chapman and Hall, Ltd., London, 1959.

(47) G. I. Samokhvalov, L. A. Vakvlova, S. G. Mairanovsiciy, and L. U. Luk'yanoka, Zhur. Obschei Khim. 29, 1936 (1959). [C. A., 54, 8611b (1960).]

(48) I. N. Nazorov, Zh. A. Krasnaya, and V. P. Vinogradov, Zhur. Obschei Khim. 28, 460 (1958). C. A., 52, 13611i (1958).

(49) E. E. Schweizer, J. Am. Chem. Soc., 86, 2744 (1964).

(50) Page 21, this thesis.

(51) Page 73, this thesis.

(52) W. J. Hickinbottom, D. Peters, and D. G. M. Wood, J. Chem. Soc., 1955, 1360.

(53) Page 54, this thesis.

(54) C. C. Sweely, R. Bentley, M. Makita, and W. W. Wells, J. Am. Chem. Soc., 85, 2497 (1963).

(55) J. Clark and J. Reed, J. Chem. Soc., 1934, 1773.

(56) J. L. Simonsen, "The Terpenes," The University Press, Cambridge, Vol. I, 1953, p. 236.

(57) A. Shimomura and J. B. Cohen, J. Chem. Soc., 121, 2051 (1922).

(58) M. D. Sutherland and O. J. Waters, Aust. J. Chem., 14, 596 (1961).

(59) T. Reichstien and A. Grussner, Helv. Chim. Acta., 16, 28 (1933).

(60) Page 60, this thesis.

(61) H. Gilman, R. Burton, and E. W. Smith, Rec. Trav. Chem., 51, 407 (1932).

(62) H. Gilman ed., "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., Vol. I, 1948, pp. 508-509.

(63) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 855.

(64) H. Gilman and R. R. Burtner, Iowa State Coll. J. Sci., 5, 189 (1931).

(65) Walter H. Hartung and Robert Simonoff, Organic Reactions, 7, 265 (1953).

(66) A. L. Mndzhoian ed., Syntheses of Heterocyclic Compounds, Vol. 1, p. 23, Chapman and Hall, Ltd., London, 1959.

(67) Reference 63, pp. 895, 901.

(68) K. Alder, H. Betzing, and K. Heimbach, Ann., 638, 187 (1960).

(69) M. S. Newman ed., Organic Synthesis, John Wiley and Sons, Inc., New york, N. Y., Vol. 40, 1960, p. 29.

(70) E. Sherman and A. P. Dunlop, J. Org. Chem., 25, 1309 (1960).

(71) R. B. Woodward and F. V. Brutcher, Jr., J. Am. Chem. Soc., 80, 209 209 (1958).

(72) N. A. Milas and S. Sussman, ibid., 58, 1302 (1936).

(73) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall Inc., Englewood Cliffs, N. J., 1965, p. 99.

(74) A. R. Gilby and D. F. Waterhouse, Aust. J. Chem., 17, 1311 (1964).

(75) J. I. Musher and E. J. Corey, Tetrahedron, 18, 791 (1962).

(76) W. Reppe, et al., Ann., 596, 110 (1955).

(77) Page 57, this thesis.

(78) Page 58, this thesis.

(79) Page 18, this thesis.

(80) Page 50, this thesis.

(81) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp. 141-142.

(82) J. Boeseken, Bull. soc. chim., France 1933, 1332.

(83) Reference 73, pages 114-122.

(84) The author wishes to thank Mr. Walter Fleming for these computed spectra.

(85) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, pp. 44-46.

(86) The author is very grateful to Mr. Allan Douglas for these spectra.

(87) Reference 44, p. 385.

(88) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 187.

(89) Reference 62, p. 828.

(90) Page 35, this thesis.

(91) G. C. Pimentel, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p. 284.

(92) J. P. Cleveland, M.S. Thesis, Georgia Institute of Technology, 1965, p. 30.

(93) J. P. Cleveland, ibid., p. 34.

(94) M. Karplus, J. Chem. Phys., 30, 11 (1959).

(95) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., R. P. Graber, and K. Folkers, J. Am. Chem. Soc., 68, 1460 (1946).

(96) R. U. Lemieux, W. J. Polglase, C. W. DeWalt, and M. L. Wolfrom, ibid., 68, 2748 (1946).

(97) R. U. Lemieux, C. W. DeWalt, and M. L. Wolfrom, ibid., 69, 1838 (1947).

(98) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p. 186-189.

(99) D. Gagnaire and P. Vottero, Bull. soc. chim. France 1963, 2779-2784.

(100) Page 52, this thesis.

(101) A. A. Bothner-By and R. E. Glick, J. Chem. Phys., 25, 362 (1956).

(102) R. W. Lenz and J. P. Heeschen, J. Polyner Sci., 51, 247 (1961).

(103) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, J. Chem. Soc., 1962, 3699.

(104) R. J. Abraham and K. A. McLauchlan, Mol. Phys., 5, 196 (1962).

(105) R. J. Abraham and K. A. McLauchlan, ibid., 5, 513 (1962).

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(107) J. A. Pople and A. A. Bothner-By, J. Chem. Phys., 42, 1339 (1965).

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